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A FUNDAMENTAL CONSIDERATION OF ANTICOAGULANT THERAPY*

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THE fundamental problem in all anticoagulant therapy is to maintain a decreased coagulability of the blood until the danger of thrombosis is past. Since as yet there is no adequate clinical test to demonstrate a thrombotic tendency, the indications for anticoagulant therapy are essentially statistical, being limited to cases in which experience has shown a high incidence of thrombosis. This varies from almost certain further thrombosis and embolism, with the patient showing frequent recurrences of these vascular accidents, to the definite but low incidence for general postoperative cases. Although anticoagulant therapy is essential for the first type of patient, it will be a matter for clinical judgment to decide the need for such therapy in the case in which the probability of thrombosis is not as great.

Having initiated anticoagulant therapy, one must decide how long to maintain it. In theory, it should be maintained until the thrombotic tendency is over. In practice, this means the subsidence of clinical symptoms. Murray[1] recommends anticoagulant therapy for eight days to three weeks, as judged by the clinical picture. However, certain patients with recurring thrombotic and embolic tendencies need anticoagulant therapy for long periods. In fact, Foley and Wright[2] consider that patients with cardiovascular diseases showing repeated attacks of thrombotic and embolic episodes should be maintained on anticoagulant treatment for years, probably for life.

Although the maintenance of a decreased clotting power of the blood will control the dangers of thrombosis, such decreased coagulability, of course, increases the danger of hemorrhage. The crux of anticoagulant therapy is careful control of the anticoagulant so as to steer an even course between the dangers of thrombosis on the one hand and the dangers of hemorrhage on the other. Two anticoagulants are in chief use — heparin and Dicumarol.

Heparin acts directly on the blood. It affects the clotting time but not the prothrombin time unless given in very high dosage. Surprisingly enough, neither anticoagulant in therapeutic doses has any effect on the bleeding time. Thus, patients under heparin therapy with very long clotting times, are still allowed to shave and so forth. Heparin must be given parenterally. It is ineffective by mouth. It acts immediately, and recovery is very rapid. This means that control of anticoagulant therapy using heparin is relatively simple. When administration is stopped the clotting time will rapidly return to normal. When a great excess of heparin has been administered through error an antidote is available in the form of protamine.

Dicumarol is an indirect anticoagulant. It acts by interfering with the formation of prothrombin by the liver. It increases the prothrombin time but has no effect on the clotting time. It does not act immediately. The latent period is about twenty-four to forty hours. It is long acting. After cessation of Dicumarol treatment, the prothrombin time may remain prolonged for as long as ten days. Hence control is not as easy if overdoses of the drug are given inadvertently. The antidote for overdosage of Dicumarol is fresh blood. Very large doses of vitamin K neutralize the action of the drug experimentally but are of less value as an antidote clinically.

The factors to be considered in the administration of anticoagulants are the measurement of the degree of hypocoagulability produced by the drug and, secondly, the maintenance of levels of the drug in the body sufficient to guarantee satisfactory hypocoagulability.

MEASUREMENT OF HYPOCOAGULABILITY DUE TO HEPARIN

The degree of hypocoagulability produced by heparin is easily judged by its effect on the clotting time. The prolonged clotting time obtained with this anticoagulant is modified by the technic of taking the blood sample, the technic used in the determination of the clotting time and various factors acting in vivo. Of first importance is the technic used in obtaining the blood sample. There are marked differences between blood from superficial veins and that from capillaries. A dose of

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heparin sufficient to produce a prolonged clotting time in venous blood has very little effect on the clotting time of capillary blood. With venipuncture, an extremely important point of technic is to make a clean stab. It is not an exaggeration to say that this is the *most important factor in determining the clotting time.* A clotting time of 15 or 20 minutes after the administration of heparin, may be reduced to 5 minutes by faulty venipunctures. In this connection, it is well to remember that repeated venipunctures can modify the clotting time. An important modification of the procedure is the use of silicone-treated syringes as described by Jaques et al.[3]

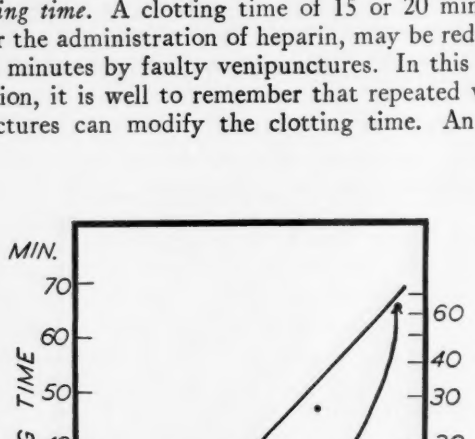

FIGURE 1. *Relation between Heparin Concentration and Clotting Time. (Reproduced from Jaques and Ricker[4] with the Permission of the Publisher.)*
x——x = clotting time.

The technic of the determination affects the clotting time. Such factors as temperature, surface, shape of vessel and movement are of great importance. A clotting time of 15 minutes may be due to 0.05, 0.15, or 1.5 units per cubic centimeter of blood, depending upon the technical conditions used. For this reason physical conditions must be carefully standardized and kept constant. If this is done, it is possible to obtain reproducible results with determinations of clotting time. As indicated by Jaques and Ricker,[4] standardization of physical conditions is necessary, but the exact standards selected should be based on the levels of heparin in the blood that one desires to measure.

The difficulties involved in the determination of clotting times raise an important question regarding all anticoagulant therapy. Should the drugs be given in terms of the decreased coagulability, or should they be administered on a weight basis? The latter ignores the different responses of patients to the drug and is therefore open to the objection that it occasionally causes a serious accident. On the other hand, if the measurement of hypocoagulability is not accurate, administration of these drugs on the basis of changes in coagulability can lead to serious accidents, as has, unfortunately, been observed on a number of occasions. Ideally, the dosage should be determined by the amount of the drug required to prevent thrombosis in the patient undergoing the treatment. To date, the fundamental data necessary to make any recommendations in this regard are lacking.

The response of the clotting system to heparin is affected by various physiologic and pathologic factors. Considerable variation is found in individual response to heparin. De Takats[5] speaks of hyporeactors and hyperreactors to heparin. These are patients who show a markedly lesser and greater response to heparin than the normal person. Other factors are anesthesia, operations, surgical convalescence, thrombotic conditions and Dicumarol simultaneously. Both Crafoord[6, 7] and Murray[1] have emphasized the fact that more heparin is required to maintain a raised clotting time postoperatively.

An important factor in the control of heparin therapy by the coagulation time is the relation between clotting time and heparin concentration.[4] When the clotting time is determined for varying concentrations of heparin, a curve is obtained (Fig. 1). Small concentrations of the drug have little effect; a further increase in concentration causes a significant rise. However, a slight increase in concentration above this level causes the clotting time to become greater than 1 hour (actually, over 24 hours). The relation between heparin concentration and clotting time is logarithmic, so that if the results are plotted on a logarithmic scale, a straight line is obtained. The nature of this relation is such that there is only a narrow range of concentrations that give clotting times in a measurable range—for example, from 0.1 to 0.25 units. To maintain a clotting time of 20 minutes, therefore, one must keep the heparin concentration in the blood within narrow limits.

Maintenance of Blood Heparin Levels

The blood heparin level represents a balance between the dose of anticoagulant administered and the factors causing its removal from the circulation. Figure 2 shows the concentration of heparin in the blood after a single intravenous injection of 4 mg. (400 units) per kilogram of body weight. It can be seen that the heparin disappears very rapidly from the blood, for 80 per cent of this dose had disappeared from the blood in an hour. A sensitive method for the determination of clotting time did not show measurable values until two and a half

hours after the injection, when the heparin concentration had fallen to 10 per cent of the original level.

The very rapid elimination of heparin from the circulation in the first hour appears to be due to renal excretion, and single large doses of 150 mg. or more are therefore wasteful. However, once the concentration of heparin in the blood has fallen to about 2 or 3 units per cubic centimeter, which represents the renal threshold, elimination of heparin is much slower, being due to the action of heparinase.[8] When the rate of disappearance of heparin from the blood is determined for various concentrations of heparin below the renal threshold, it is found that the rate decreases in proportion to the concentration of heparin in the blood.[9]

As already indicated, heparin must be given parenterally. The two original groups of workers differed somewhat in that the Toronto group preferred a continuous intravenous injection, whereas the Swedish group preferred single injections at frequent intervals. Actually, the difference in the two methods is relatively minor. The continuous injection provides a closer control over the anticoagulant, avoiding periods of incoagulability alternating with periods of nearly normal clotting. Provided the next injection of heparin always overlaps the effect of the previous injection, however, control of thrombosis is equally achieved with single injections. In connection with single injections, Hedenius[10] describes a hypercoagulable state occurring if heparin is withdrawn too suddenly and recommends gradual withdrawal.

For continuous administration approximately 20 mg. per hour is given to establish a clotting time of 15 minutes. Murray recommends 200 mg. in 100 cc. of saline solution to be infused at the rate of 30 drops a minute until the clotting time reaches 15 minutes and then reduced (usually to 20 drops a minute) to maintain the clotting time at this level. Postoperatively some change in rate is required with time.

The Swedish group recommend administration of heparin in four daily doses, 3 of 50 mg. during the course of the day starting at 8 a.m. and the fourth dose of 100 mg. at 8 p.m., making a total of 250 mg. for twenty-four hours. In some cases, however, it is necessary to give three doses of 75 and one of 125 mg. daily. The objection to frequent venipunctures can be largely overcome by the use of an Olavson needle. This needle is allowed to remain in the vein (sufficient heparin being retained in the needle to keep it free of clots) and is held in place by adhesive tape. The needle is provided with a detachable cap with a rubber membrane, through which injections are given, and thus intravenous injections can be made at any time, even at night, without discomfort to the patient. An improved pattern has been developed by Heyman (the Olavson–Heyman needle).

Since the action of heparin on intravenous injection is fleeting, attempts have been made to develop heparin that could be used either intramuscularly or subcutaneously to provide a depot type of anticoagulant. Both the Swedish workers and the Toronto group in their early work tested subcutaneous injections but did not recommend this method of administration since it was found that the effects were variable and also that a given dose of heparin was much less effective on subcutaneous injection than by vein. Loewe et al.[11] have attempted to improve the subcutaneous administration of heparin by means of the Pitkin menstruum. Any improvement in the effect of

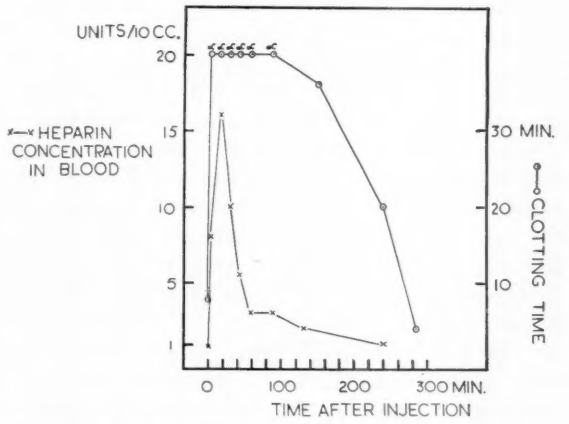

FIGURE 2. *Heparin Concentration in the Blood after Injection. x——x = Heparin concentration; o——o = clotting time.*

heparin on the clotting system by the use of this menstruum does not seem to compensate for the pain and other difficulties arising from this procedure. A more practical approach to the problem appears to be that of Stats and Neuhof,[12] who made use of very concentrated solutions of heparin to reduce the volume and thereby to control absorption. Stats and Neuhof employed intramuscular injections, previously given successfully by Rhoads, Walker and Panzer. For subcutaneous or intramuscular injections, 100 mg. every eight hours is required. Vorzimer, Sussman and Marder[13] have recently improved this procedure by incorporating the heparin in an oil emulsion so that the amount required for twenty-four hours can be given in a single injection.

Various substitutes for heparin have been suggested. These are chiefly polysaccharides with attached sulfuric acid groups, although acid dyes such as chlorazol fast pink and germanin have been tested. Jorpes, Wilander, Astrup, Todd, Seifter and Begany, and Wright have used various sulfonated polysaccharides.[14]

Since the most active of these substances has only one seventh of the activity of heparin much larger amounts must be given. Also, heparin is a normal constituent of the body and therefore the body has mechanisms for metabolizing it, but mechanisms may not be available for the metabolism of these foreign polysaccharides. Hence there is a possibility that storage of these materials in the liver and elsewhere will lead to later toxic effects. However, it is possible that one or more of these substances will be found that can be metabolized by the body and will therefore have no long-term toxicity.

Measurement of the Hypocoagulability Due to Dicumarol

The hypocoagulability of the blood following administration of Dicumarol is due to the decrease in blood prothrombin. In contrast to the heparinized patient, there is no increase in the clotting time after Dicumarol. Actually, this apparent paradox is due to the artificiality of the determination of clotting times in glass vessels. Moloney, Murphy and Harrington[15] and Margulies and Barker[16] have shown that if the clotting time is determined with the use of silicone-coated syringes and tubes to avoid the effect of glass, a very marked decrease in the coagulability of the blood results from the administration of Dicumarol. In addition to the fall in prothrombin, Fahey, Olwin and Ware[17] have shown that there is a moderate decrease in accelerator globulin for the first two weeks on Dicumarol therapy, followed by recovery. However, the fall in the prothrombin concentration in the blood is the significant effect.

Methods for the Estimation of Prothrombin[18]

The fall in prothrombin after administration of Dicumarol is measured accurately by the two-stage prothrombin titration of Warner, Brinkhous and Smith.[19] In this the sample of plasma is defibrinated, and the prothrombin in the plasma, after dilution, is converted to thrombin with thromboplastin and calcium. The total thrombin formed is then measured by its clotting of fibrinogen. When the combined reagents become available commercially, this method will be generally available for clinical use. With the addition of accelerator globulin (modified two stage) it gives an accurate measure of prothrombin concentration in the blood.

Although the most accurate method of measurement of prothrombin is the modified two-stage technic, for routine control it is probably more important to have some general measure of the extent of the hypocoagulability produced by this drug. Various modifications of the shortened clotting-time test (made popular by Quick[20] under the name "prothrombin time") appear to be suitable for this purpose. The test as devised by Quick consists in determining the clotting time of 0.1 cc. of oxalated plasma and 0.1 cc. of 0.02 molar solution of calcium chloride and 0.1 cc. of rabbit-brain extract. Disadvantages of this test include the fact that the system is not sensitive to slight decreases in prothrombin. In fact the method does not show any change in the value until the prothrombin concentration has fallen to below 50 per cent of normal (Link[21]), and with Dicumarol, this means that the prothrombin time will be approaching hemorrhagic levels before the action of the drug can be discontinued. Secondly, as first shown by Jaques and Dunlop,[22, 23] the prothrombin time after administration of Dicumarol is very sensitive to the concentration of calcium ion. This means that failure to maintain an exact control of the oxalate and hence the calcium concentration present in the test can lead to serious errors; also, owing to the concentration of calcium used by Quick, his test fails to reveal the hypocoagulability actually existing with a given blood sample. Thirdly, the blood sample for the determination of the prothrombin time by Quick's method is, in general, taken at the same time as Dicumarol is administered. This means that values obtained for a prothrombin time for a given day are not employed to correct the dosage until twenty-four hours later.

The Link–Shapiro[24] modification is in very general use to overcome some of these defects. It consists in preparing a modified thromboplastin extract and usually determining the prothrombin time with both undiluted plasma and with plasma diluted 1:8. Schwager and Jaques[25] have developed a method for determining the prothrombin time of whole blood at the bedside based on the method of Ziffren et al.[26] This is particularly useful in small hospitals and in office practice. The rabbit-brain extract is prepared in sealed capillary tubes and kept frozen. A sufficient supply for three to six months can be made at one time. A tube is broken, melted and placed on a watch glass. Four drops of blood, obtained by clean venipuncture, is added and mixed, and the clotting time determined by the observation of when a fibrin thread can be lifted by the needle. As no anticoagulant is added this method uses the patient's own calcium.

The most difficult part of a determination is the preparation of thromboplastin. Even when an active thromboplastin extract is used, giving a value of 12 seconds with normal plasma as required by Quick, this is no guarantee that the values obtained after administration of Dicumarol will correspond to the concentrations given by Quick. The dried rabbit-brain powder now available commercially is satisfactory for the preparation of the thromboplastin extract, but most workers have encountered unexplainable variations in the extracts themselves.

Olwin[27] has conducted simultaneous determinations of prothrombin concentration by the two-stage titration and of the prothrombin time by the

Quick[20] and Link–Shapiro[24] methods, which demonstrated marked and independent discrepancies with the two-stage procedure. At times when the two-stage technic showed that the patient was well standardized with prothrombin levels 10 to 20 per cent of normal, the Quick or Link–Shapiro method revealed a swing back to temporary normal values. Since such an approach to normal values suggests that the patient is escaping from the action of the Dicumarol, if one of these methods were used alone, the Dicumarol dosage would be increased, with danger of hemorrhage. It is possible, as Olwin suggests, that cases of fatal hemorrhage following administration of Dicumarol have been due to such erroneous prothrombin estimations. The errors may be due to variations in factors, other than the prothrombin concentration, that affect the prothrombin-time estimation as well as actual technical errors. As an example of such errors Foley and Wright[2] discuss a patient on Dicumarol therapy referred to them with a reported prothrombin time of 27 seconds who actually was shown to have a prothrombin time of over 300 seconds. It is evident that the determination is far from a simple laboratory procedure. It may be that the whole-blood prothrombin time will avoid some of these difficulties.

When the method was first introduced, it was frequently customary to express the results as a percentage of the ratio of the value for patient's plasma to that for normal plasma. As a result of the work of many workers, it is now realized that this method is quite erroneous. The factors involved in the determination of prothrombin time and the relation between prothrombin time and prothrombin concentration are too complex for such simple treatment. Quick[20] recommended the use of a curve to convert prothrombin times to prothrombin concentrations, obtained by determining the prothrombin time of various dilutions of normal plasma. However, the work of Seegers,[28] Owren,[29] Olwin,[27] Jaques and Dunlop[22, 23] and others has shown that Quick's assumption that the prothrombin time of diluted plasma corresponds to the values obtained for a corresponding decrease in prothrombin is not justified when this decrease is due to the action of Dicumarol, and that the assumption can lead to gross errors in the estimation of prothrombin concentrations. The least objectionable method is to express all values as actual seconds of prothrombin time. Then, provided a reasonably standardized thromboplastin has been used, the values can be grouped into zones. For a thromboplastin giving a normal prothrombin time of 12 seconds, therapeutic levels of Dicumarol correspond to prothrombin times of 17 to 37 seconds, with hemorrhagic levels above 37 seconds. For the whole-blood prothrombin time the corresponding values are 23 to 25, 34 to 52 and more than 52 seconds. As indicated, values for these levels are changed by changes in the method, particularly the thromboplastin. Furthermore, too much reliance should not be placed on these ranges. Hemorrhage may occur with prothrombin times under 40 seconds and may not occur even with very prolonged values. Finally, the value should be determined and reported simultaneously for a sample of normal blood, and the value for the patient on a given day interpreted in the light of all other values reported for him. Any sudden gross change in the values obtained should arouse suspicion regarding the technic of the determination.

Maintenance of Dicumarol Levels

Although it has been generally believed that Dicumarol acts on the liver to prevent prothrombin synthesis, the first direct evidence for this has only recently been supplied by Lupton,[30] with the demonstration that the liver from an animal treated with Dicumarol, in contrast to the normal liver, fails to maintain the prothrombin level of blood perfused through it. In the past few months at the University of Saskatchewan, Lee et al.,[31] in the Department of Chemistry, have obtained direct evidence for the action of the anticoagulant in the liver by studies of Dicumarol levels in the body after administration. This has been possible through the preparation of labeled Dicumarol, in which radioactive carbon, C^{14}, has been incorporated in the molecule. As shown in Figure 3, rabbits were given a single dose intravenously of 5 mg. per kilogram of body weight, corresponding to a clinical dose of 350 mg. It can be seen that after a lag period of about forty-eight hours the prothrombin time rose

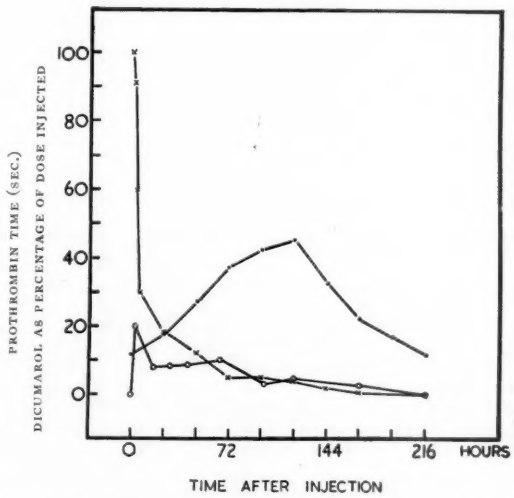

FIGURE 3. *Concentration of Radioactive Dicumarol in Rabbit Tissues (o——o = Concentration in Liver, x——x = Concentration in Blood, and .——. = Prothrombin Time). Dicumarol, 5 mg. per kilogram of body weight, was given intravenously at zero time.*

to a peak in seven days. It then gradually decreased and reached normal values in eleven days. The concentration of Dicumarol in the blood, liver and other organs was determined. The intravenous injection resulted in the immediate dispersal of the injected Dicumarol in the circulation. Sixty per cent of the injected Dicumarol was still present in the blood four hours after the injection. However, by the twenty-fourth hour only 12 per cent remained, and by the time the prothrombin time

FIGURE 4. *Concentration of Radioactive Dicumarol in Mouse Liver (x——x = Concentration after 5 mg. of Dicumarol per Kilogram of Body Weight Intravenously, and o——o = Concentration after Simultaneous Injection of 5 mg. of Dicumarol and 1 mg. of Vitamin K per Kilogram of Body Weight). (Reproduced from Lee et al.[31] with the Permission of the Publishers.)*

reached peak value, the blood level of Dicumarol had fallen to half of 1 per cent of the total dose.

No significant amounts of the drug were found in any tissues except the liver. Four hours after the injection 20 per cent of the material injected was found in the liver. The concentration of Dicumarol in the liver fell to 10 per cent and then remained at this level for some time. There was a further fall, but when the prothrombin-time value was at its peak, 2.5 per cent of the injected Dicumarol was still in the liver.

These results explain a long-standing paradox in the literature — namely, that recovery of prothrombin levels after the administration of Dicumarol requires seven to fourteen days, whereas recovery of these levels takes only twenty-four hours when there is temporary interference of this function of the liver by withdrawal of vitamin K and so forth. The slow recovery of prothrombin levels following administration of Dicumarol is due to the fact that the drug remains in the liver.

As shown in Figure 4, the effect of vitamin K on the action of Dicumarol is also related to storage in the liver. This shows the concentration in liver after injection in mice; 12 per cent of the injected Dicumarol was found in the liver an hour after injection and remained there for twelve hours. On injection of the same weight of vitamin K along with the Dicumarol, the same amount of Dicumarol went to the liver, but in the presence of the vitamin K, the concentration of Dicumarol in the liver decreased immediately.

The commonly accepted dose of Dicumarol is 300 to 400 mg. initially, followed by a single daily dose thereafter. The daily dose is adjusted to maintain the prothrombin level at approximately 20 per cent of normal (prothrombin time of 27 seconds), on the basis of the daily prothrombin times. Peters and his associates[32] consider that it is unnecessary to maintain the prothrombin this low, and that 35 to 50 per cent of normal is adequate to prevent thrombosis, with less danger of hemorrhage.

Regarding the maintenance dose, Olwin[27] states that most of his patients require 250 to 450 mg. a week, but he emphasizes the fact that there is no

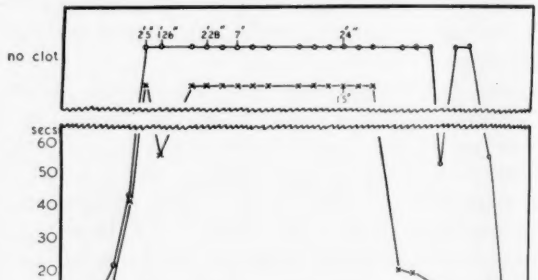

FIGURE 5. *Effect of Repeated Doses of 16.3 mg. of P.I.D. per Kilogram of Body Weight Every Eight Hours on the Prothrombin Time of Dogs (o——o = Dog Sa; x——x = Dog Sp).*

such thing as an average patient so far as Dicumarol therapy is concerned. Each case must be standardized separately and checked frequently to make sure that there has been no change in the response to Dicumarol.

The response to Dicumarol is affected by a number of factors. There is now evidence, either experimental or clinical, that the following factors have an influence: genetic constitution, nutritional status (fasting, protein intake, vitamin K and C levels in the diet and body reserves), pre-existing hypoprothrombinemia (salicylates, chloroform anesthesia and so forth), presence of drugs that affect the total functioning capacity of the liver (methylxanthines, digitalis and so forth), alcohol, and pregnancy and lactation.[2, 18]

The greatest disadvantage with Dicumarol is the fact that recovery from the drug is very slow.

Hence, if hemorrhage results from inadvertent overdosage, the danger of further hemorrhage persists in spite of measures taken to combat it. Since the long action of Dicumarol is due to the fact that the drug remains in the liver for a long period, it may be possible to find substances that act similarly but are metabolized more rapidly and thus to avoid the dangers of Dicumarol therapy. Three compounds up to date appear to have been developed for this purpose. Fantl,[33] in Australia, has reported on the ethylidene analogue of Dicumarol. This is less active than Dicumarol, but recovery is more rapid. European workers, particularly von Kaulla,[34] have used the acetic acid ethyl ester of Dicumarol. This appears to have approximately the activity of Dicumarol but gives more rapid recovery. Soulier[35] and Jaques et al.[36] have studied another compound, phenylindanedione (P. I. D.). This compound, although only remotely related to Dicumarol, is an effective prothrombopenic agent. As shown in Figure 5, the administration of 50 mg. per kilogram of body weight daily to rabbits will result in very prolonged prothrombin times (over 1 minute). Cessation of the administration of the drug results in a return of the prothrombin time to normal in twenty-four hours. This effect is remarkable when it is considered that it takes ten days after Dicumarol administration for similarly high prothrombin times to return to normal. So rapid is recovery from this compound that it is advisable to administer the drug two or three times a day in divided doses. Furthermore, if one dose is missed the effect is observed in the prothrombin-time record. This compound appears to be reasonably free of toxicity as determined in long-term animal tests.

Blaustein[37] has used this material clinically on 35 patients. In clinical dosages the material appeared to be as effective as Dicumarol. In addition, it showed a more rapid effect on the prothrombin time and produced the same rapid recovery of prothrombin time as in the animal experiments. The longest time for recovery to occur was forty hours. Owing to the differences in body size and in the metabolism of the drug, it appeared that it might be easier to stabilize the human beings than the animals. It is probable that the same factors that affect the response of the liver to Dicumarol are effective with phenylindanedione. No signs of toxicity were observed by Blaustein.

Conclusions

The purpose of anticoagulant therapy is to maintain a condition of reduced coagulability of the blood, in order to reduce the danger of thrombosis. Since reduced coagulability introduces the danger of hemorrhage, it is essential to control the degree of hypocoagulability. With heparin, maintenance of hypocoagulability depends on adequate blood levels of the anticoagulant, whereas with Dicumarol, it depends on adequate levels in the liver. Control over these levels can be obtained by determinations of the coagulability of the blood itself — determinations of the clotting time for heparin and of the prothrombin time for Dicumarol.

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MANAGEMENT OF THE NEUROTIC PATIENT*

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THE neurotic patient is a troubled person. His problems are personal and may or may not be a matter of conscious knowledge. The symptoms that occur as a result of these problems may be physical sensations and changes in physiologic function, often simulating organic disease, or disturbed states of mind, with anxiety, doubt and ineffectiveness as common complaints.

The task is to discover and define the ideas, fears, errors in belief and emotional conflicts that have produced the problems and disturbed the smooth functioning of the patient in achieving some constructive purpose in life.

In a psychiatric interview no attempt is made to ask specific questions. To do so might give the impression that the doctor will decide what he wishes to know and be content with answers that supply this information. An hour is allotted to each interview in order that the patient may relax with a realization that the doctor's attention is completely at his disposal, for sufficient time to encourage conversation.

The patient is asked to give his own version of what the trouble may be and any facts about himself or the situation that seem to be reasons for it. In the verbal expression of thoughts, fears and beliefs they acquire tangible definition that often for the first time permits a rational consideration. There is also relief of mental tension in getting the trouble out of the mind in an objective form in which it can be appraised and the responsibility of what to do shared by another person, who is trusted to understand rather than judge. In telling the story of his need for help, the patient supplies data for a preliminary estimate of his personality structure, the resources he has mobilized to deal with difficulties and his sensitivity and relative degree of emotional maturity. It is essential to distinguish whether the patient is comparatively healthy minded and dealing with an unusual and trying situation, or is unstable, poorly integrated and in difficulty because of a fundamental lack of adaptive technic and inability to deal with ordinary life situations with perception, respect for reality and emotional response appropriate to the facts. There is considerable variability in the need for help, the kind of help that will be most effective and, sometimes even more important, the capacity of the patient to accept or tolerate being helped. One's judgment of these variables will determine what course to pursue.

Therapy tends to have one of two general purposes. In the first place it may be designed as supportive. If the patient's personality is considered adequate or, on the contrary, too insecure for exploration to be risked, one may elect to mobilize the existing resources of strength and determination, inhibit anxiety and restore emotional equanimity and self confidence, clarify the situation, indicate ways of tolerating the facts and stimulate courage to deal with the difficulties. To this end, direct reassurance, suggestion, inspiration, persuasion and education may all serve as useful aids. The confidence, optimism and authority of the physician play an active role in such an approach. A doctor who inspires the statement "I feel better as soon as he comes in the room" has a therapeutic potential, often functioning without conscious intent but highly supportive in effect. In psychotherapy an effort is made, intelligently and consciously, to employ this kind of help in order to create an emotional climate in which the patient's anxiety is reduced and his resources, both physical and mental, can be used to better advantage.

The second purpose is to attempt to change fundamental habits that have controlled behavior. To this end one must acquire an understanding of the experiences and subjective states of mind that were effective in producing the patient's character. Habits and beliefs are established by experience with real situations and real people, but in childhood there is a limited capacity for interpreting the relations correctly. Hence errors in judgment and opinion may be incorporated in ways of reacting, designed to solve early problems. The child, furthermore, conceives situations as static and tends to feel a finality about his interpretations that precludes easy change of attitude. He acquires an illusion of knowledge in very simple terms, when the truth is really complex and relative. For information about these early mistakes, it is necessary to explore the patient's early memories, recreate important experiences and the nonverbal assumptions contingent on them, reactivate his relations with parents, siblings and people and try to bring to consciousness feelings and ideas about himself and life in general as they existed in childhood.

For any change of character to be effected, one must first accept how much present behavior is in fact determined by past experience and habits that give direction to the behavior with compulsive intensity, usually too rapidly for any exercise of conscious choice. Habits are initiated to serve some purpose. To have a habit cease, it is essential to

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realize that the initial purpose was falsely conceived, or that it is no longer valid or useful to the mature personality. In therapy one attempts to learn the conditions determining the origin of habits and the possible errors involved. It is then necessary to devalue the present desirability of the purpose and to alert the mind to a conscious sense of the habit as operative before it discharges and a toleration of having to check its repetitive attempts to function.

To co-operate in such a purpose the patient must have a capacity for introspection, intelligence, the ability to tolerate painful revelations about instinctive motivation and sufficient mental distress to sustain a strong desire to change his way of life.

There is little wish to alter the psychic balance that permits relative mental comfort. Mental distress is a challenge to risk more pain in the hope of increased freedom of action and a happier state of mind. In this sense emotional suffering may be considered desirable for the therapeutic situation since it creates a condition favorable to learning and growth.

The physician who hopes to help the neurotic patient needs the heart for emotional rapport that assures sympathetic appreciation of the patient's painful experience, intuitive or trained skill in encouraging the production of pertinent material and its interpretation, the poise and authority to inspire the confidence that he can, and will in some way, take care of any immediate crisis until a safer equilibrium is established, and endless patience.

Between the physician and the patient there is a constant attempt to clarify why the patient feels and reacts in ways detrimental to his best interest or conscious purpose. What obstinacy or misinterpretation perpetuates defensive attitudes as though the world were filled with hostile people? What manner of self-appraisal has left such feelings of guilt and shame? Why the compulsive activity and striving toward ideal goals with so little or no pleasure either in the doing or in the achievement? Why the anxiety, depression and apprehension that tend to invade a period of relaxation? Explanations usually are found in the life of the child, who, with no experience, not knowing how or what to ask, or even daring at times to inquire, supplied answers to his ignorance from his own imagination, establishing fantastic convictions about himself and what to expect in life. These beliefs have not been given conscious verbal form and must be sensed or inferred from the nature of the behavior and the feelings that went with it. The patient is encouraged to be honest with himself about emotions that various situations arouse in him, rather than to screen his feelings and register only what he believes he ought to feel in terms of socially accepted ideals. His pitch of voice, inflection, hesitation or rapid change of subject is often evidence that a nucleus of mental conflict is influencing what is being said.

Motor restlessness, irritability or disturbed physiological function, such as sweating hands, blushing or need to go to the bathroom, may give further evidence that the interview is producing critical emotional tension. Phenomena of this kind suggest the activation of impulses to act in ways that are antisocial and frightening, personal attributes associated with a sense of shame or guilt or some disturbing memory. In other words, the behavior is appropriate to a subconscious state rather than the actual verbal communication or immediate situation. All people create blind spots for facts about themselves that they might consider reprehensible and rationalize their opinions and actions so that they remain confident that they are intelligent human beings with freedom of will, masters of their fates and captains of their souls. In these troubled patients such a defensive system has ceased to be completely successful. Some stress has become too great for effective adaptation, producing a threat to the façade of self-approval that is essential to a sense of dignity, pride and peace of mind. Human relations involve problems of pleasure, pain, love, hate, jealousy, envy, greed, security and status that are very real. In addition to being subjectively experienced, they can be defined and viewed objectively in terms of their appropriateness and value. So too the fears, conflict and complex motivations that emerge as a result of their functional activity can be subjected to definition and appraisal. Neurotic behavior implies that somewhere something went wrong. The task is to find it and, through a more mature knowledge, to recognize the error as error but legitimate to the child's lack of experience and the nature of the real situation. In this way the error need no longer be repressed but can be accepted and deprived of further power to influence present behavior.

In neurotic patients certain tendencies occur with unusual frequency. There is a tendency to endow thoughts, ideas and feelings with much more value than facts that are registered perceptually. The capacity for sustained attention to the objectively real world outside them is often low. They are quick to jump to generalizations from very limited and often faulty observation and defend their generalizations as though their life and integrity were at stake. A single experience is often enough to establish conviction about what must inevitably be expected in the future.

They are like the little boy who, full of warmth and affection, ran toward a lady who was calling on his mother, only to be told, "Go away; I don't like little boys." Deeply hurt, he thought, "Women hate me — I'll never trust one again." Later, a more kindly soul attempted to be friendly, but he withdrew in fear. The friendly approach was conceived as only an opening gambit for the rejection he now assumed was inevitable. There is intense

resistance to being open minded when the possibility of having one's feelings hurt is at stake.

Another common tendency in the neurotic person is the absorption of mental energy in unconscious phantasy. The reality of this possibility may be demonstrated through the consideration of a relatively familiar experience. While supposedly reading a book, one's eyes may follow the words line after line, but at some point one becomes aware of having no knowledge of what the eyes have brought to the mind. The honest answer to the question of what one has really been thinking about is usually "I don't know" or "Nothing." There has been a blank in the continuity of conscious awareness. If in a similar situation, at the moment of turning a page, one will actively focus attention inward, on what is going on in the mind, one may often catch the tail end of some line of thought or preoccupation as evidence that during such a blank period there has been considerable organized activity going on at a so-called subconscious level. This may happen to anyone at times, but in the neurotic person this form of dissipation of energy is excessive. An examination of its content may be of great value in an understanding and interpretation of peculiarities of behavior.

Quite apart from unconscious phantasy considerable mental energy may be lost in day dreams that are conscious. Imagination can create with vividness and exquisite perfection a state of affairs in keeping with one's wish. There is no frustration. Time and hard work are no longer essential to the fulfilment of ideal hopes and one's personal concept of justice can prevail. There need be no tension of waiting, no doubt and no need to learn through the painful process of making mistakes. But this type of satisfaction is bought at a price. It is personal and lonely and foregoes the glow of social recognition. It also lacks the organic resonance of sensory components that accompany experience in which the body is physically involved.

The state of mind aroused by a perfect swan dive performed in imagination is quite different from that of the body plunging into real water. As an artistic success the phantasy may be more perfect, but as an experience it will lack much that is instinctively desired for complete satisfaction. This is true not only in quality but also in the absence of the thrill inherent in the chance of bettering a previous performance. In the phantasy there is no incentive to growth or learning.

Furthermore, if the content of imagination is taken as valid when it is pleasurable, it must be equally so for the fears, doubts and disturbing images that can be evoked. Endowing imagination with too much value can be a serious handicap to successful living. As a solution for frustration it tends to make one increasingly impatient, resentful of the limitations imposed by the real world, distressed that other people do not share his own self valuations, and abnormally fearful.

Once a patient becomes aware of the degree to which his mind has been prostituted to the ends of wishful thinking or unconscious phantasy, the obvious advantage of a more mature use of mental energy can encourage a search for reasons why this form of activity has continued. Intellectual recognition of its undesirability does not in itself terminate the habit. Its persistence implies some continuing wish for which it has been accepted as a fulfilment. It is important to define this wish, accept it as real and deal with it as a recognized competitor for energy. With this insight, the patient may consciously devalue or transcend the wish and be free to choose some other goal that is of more value to the adult self.

It may be with reluctance, but the opinion "Thought has power to make things so" must be abandoned in favor of "Thought is a tool to register what is so." It is also necessary to relinquish the naïve idea that analogy is equivalent to identity, if there is to be any logical thinking. The child in one's mind has to be educated through friendly understanding to "give up" in the interest of the mature self.

To admit error or relinquish a project as beyond one's ability does involve an admission of human limitation, but need not imply a complete personal failure.

A child is too prone to consider his entire worth at stake in every situation and has to learn that life is not frozen in a static moment. An episode, in time, can pass, leaving him wiser but not wrecked because of a painful experience. Disappointment is a recurring source of mental pain, and it is of primary importance to learn that the pain of disappointment is by its nature limited in time and intensity. A common hindrance to this learning is that during the experience, fear may arise that the pain will continue with increasing intensity to a point where it will be unbearable. This fear may produce some extraordinary mental gymnastics in an effort to terminate the pain by a trick of thinking. As the pain does stop it is quite easy to believe that the defense has saved the organism from disaster. But such a belief leaves the mind with a completely irrational fear of mental pain. Since it is remembered as a serious hazard, some mental anesthetic must be ever ready in the psychic first-aid kit, and extreme vigilance must be exercised to avoid any situation that might lead to disappointment.

If the child does not learn that it can stand mental pain, it will fail to learn that it can tolerate not having what it wants. This may lead to a stubborn tenacity about having its own way or, in reverse, a rejection of having any way of its own, because of the threat of possible frustration. This can

seriously impair the child's initiative and accentuate its dependence on authoritative direction.

From neurotic patients one frequently hears the complaint "I don't know which way to turn" or "I don't know what to do," with an obvious appeal for direction. There is a wish to avoid the responsibility and possible disappointment inherent in experimental action, while retaining the possibility of praise and acceptance by conforming to the suggestions made. At the same time, partial intuitive recognition of the dependency may be expressed in self-depreciation, feelings of inferiority and insecurity or active rebellion at any attempt to supply the guidance that is sought.

The self-regarding faculty is often a locus of trouble in the neurotic person. Self-love and selfishness are considered undesirable. Self-assurance and self-confidence are good. To achieve the proper degree of self-approval and for the right reasons is quite a problem. Without some self-satisfaction there is no core of value as an independent entity to assure one of being lovable and having a capacity to love. Insecurity in this belief can cause abnormal concern in relations with other people. Reassurance is sought but rarely believed; criticism and blame are expected but resented. Such a state of mind does not encourage mature and friendly relations but invites pity, toleration, or annoyance. This tends further to aggravate the patient's distrust and doubt of his own value, and to produce a sour-grapes attitude, withdrawal from social contacts or a stubborn, opinionated, hostile aggressiveness. When the child and adolescent have experienced so much spontaneous hostility in reaction to the frustrations and disciplines imposed by socializing forces, it is quite understandable that hostility is expected in return. But there have also been experiences of being loved and taken care of, with a desire to reciprocate in kind — hence confusion and need to understand and find some solution for the ambivalence of emotion occurring in many relations.

The sexual instinct is an inherent biologic drive with strong motivating power that exists throughout life, influencing behavior in many variable ways. The problems resulting from this drive in the infant and child are quite different from those of the adult but demand solution, and the nature of the solution influences later development. The child has much sensual interest and pleasure in nursing, eating and body functions. This spontaneous enthusiasm is found to be subject to parental and social interference necessitating modulation and control if the desire to experience acceptance, love and a sense of belonging is to be fulfilled. This initiates a conflict of wishes and constitutes a very early psychic problem.

In adolescence biologic maturation brings the power of reproduction into function. Strong emotional and physical sexual interest is aroused, and a new integration of the complex emotional potentials related to sex is essential. If the early training has been too rigid, the defenses and controls established in relation to sensual pleasure and curiosity may be reactivated. If it has been too lenient the need for control may be overwhelming in its urgency. In either event unintelligent early training may result in serious conflict and disturbances of behavior at this period. In attempting to resolve residual difficulties in adult neurotic patients, a review of the facts in these earlier phases of development may shed light on the present trouble. Life should progress with happy enthusiasm and a sense of adventure in growing up. Courage and a capacity for objectivity are essential to success, and one is constantly alert to conditions or beliefs that might interfere with the dominance of these qualities in the individual's relations with the outside world.

Conclusions

One may note that the problems presented in the management of the neurotic patient are in large part the result of emotional immaturity and poor mental hygiene. The explanation for this exists in a failure to solve the universal problems of childhood successfully. One may attempt to make the condition tolerable and salvage what effectiveness is possible under the circumstances or to reactivate the basic problems with the hope of rectifying the mistakes. The root disturbances involve security, integrity and status, particularly concerning dependence and independence, passivity and aggression, competition, sexuality, hostility and love. In nature there are powerful forces working to the end of growth and maturation. Segmental retardation is reversible. If interference is removed the patient can grow up to a realization of his initial potential.

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CALCIFIED LEIOMYOMA OF THE STOMACH*

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A LARGE, circumscribed, radiologically opaque mass within the left upper quadrant of the abdomen presents an interesting diagnostic problem. The following case has taught us to include calcified leiomyoma of the gastrointestinal tract in the differential diagnosis of abdominal calcification.

Case Report

J. A. (J.C.M.C. 365,965), a 54-year-old mechanic, entered the Jersey City Medical Center on April 25, 1946, complaining of abdominal pain that had begun 3 weeks before admission, when he noted persistent dull pain in the left upper quadrant and constipation. He was placed on a soft diet by his physician, and the pain disappeared for approximately 10 days. Since that time the pain had persisted, and the patient became aware of an upper abdominal mass and noted a recent weight loss of 30 pounds. There had never been nausea, vomiting, hematemesis or melena.

Figure 1. *Barium-Filled Stomach, Showing the Calcified Mass at the Lesser Curvature Causing a Smooth Filling Defect.*

The past history included a brief period of hospitalization in 1922 for "being run down." A benign skin tumor of the left upper portion of the abdomen had been removed in 1945. The family history was noncontributory.

Physical examination revealed a well developed man with evidence of weight loss but in no acute distress. The positive physical findings were limited to the abdomen, which was flat and soft. Within the left upper quadrant was a hard, fixed 5-cm. mass, with tenderness to pressure on its lateral aspect.

The temperature was 98.6°F., the pulse 94, and the respirations 20; the blood pressure was 138/82.

Examination of the blood showed a red-cell count of 4,500,000, with a hemoglobin of 13.5 gm. per 100 cc., and a white-cell count of 11,500, with 85 per cent neutrophils and 15 per cent lymphocytes. The urine was normal; the fasting blood sugar was 80 mg., and the blood nonprotein nitrogen 30 mg. per 100 cc.

Roentgenograms of the barium-filled stomach (Fig. 1) revealed an extensive filling defect involving the middle gastric region and represented by a "pepper-and-salt" appearance that was apparently due to calcification of the lesion. The lesion was anterior to the stomach in the lateral view. At 6 hours there was a slight residue in the stomach, and the calcific density was constant.

During the 1st week of hospitalization the pain remained severe and required codeine for relief. Because swallowing food often aggravated the pain, the patient ate very little and had no bowel movements until given magnesium sulfate and an enema on the 5th hospital day.

On the 8th hospital day laparotomy under cyclopropane anesthesia, through a left-upper-rectus-muscle incision, revealed a grapefruit-sized, hard mass lying on the lesser curvature of the stomach and adherent to the inferior surface of the liver and to the omentum. The distal two thirds of the stomach, including the tumor, was removed, and a gastrojejunostomy completed. The abdomen was closed in layers without drainage. During the 2nd to 5th postoperative days there was an average temperature of 101°F. Otherwise, con-

Figure 2. *Gastrectomy Specimen Opened along the Lesser Curvature, Showing Smooth Mucosa Covering the Tumor.*

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valescence was uneventful, and the patient was discharged on the 10th postoperative day.

Follow-up examination on June 15, 1949, showed him to be symptom free and in good health, but there had been no gain in weight.

The resected portion of the stomach measured 23 cm. in length along the greater curvature, 15 cm. along the lesser curvature and 7 cm. in width at the proximal divided end. Within the wall of the lesser curvature, extending superiorly and medially, was a hard, irregularly round 8-cm. mass, which was covered externally with smooth serosa. The mucosa overlying the mass (Fig. 2) was smooth except for a sinus tract, 0.5 by 0.3 cm., which led into the center of the hard tumor. On section the mass was circumscribed and white and presented many areas of calcification and central purulent areas of necrosis (Fig. 3). Culture of the purulent contents disclosed nonpathogenic gram-negative bacilli and *Streptococcus faecalis*.

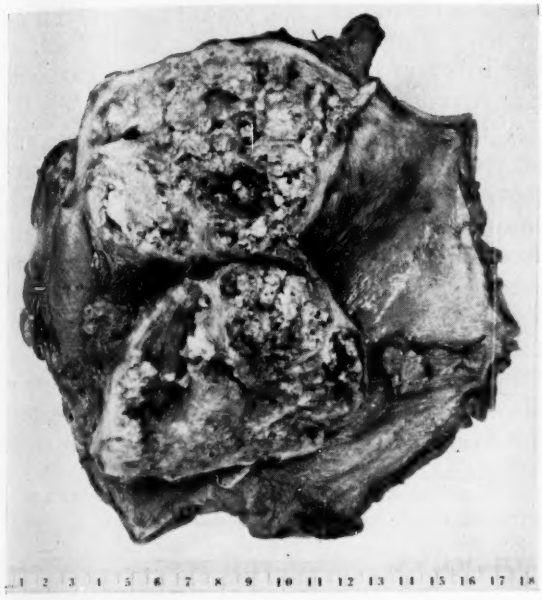

FIGURE 3. *Gastrectomy Specimen from the Serosal Surface, with Cut Surfaces of the Tumor.*

Microscopically, the tumor was composed of bundles of smooth muscle, with large irregular basophilic areas of calcification. There were areas of acute inflammation that did not seem related to the areas of calcified muscle fibers. The gastric mucosa was normal except for inflammation on the margins of the sinus tract.

DISCUSSION

Benign gastric myomas have been observed with increasing frequency during recent years on the basis of sudden severe hematemesis or chronic blood loss with the roentgenologic demonstration of an intraluminal projecting smooth mass with a central small mucosal ulcer or sinus. Golden and Stout[1] reviewed the surgical pathology of the lesion and noted that some of these leiomyomas become infected and necrotic and may perforate. Meissner[2] observed occasional small calcified gastric leiomyomas among post-mortem material and in comparing them with uterine leiomyomas wrote, "not only is the structure identical, but the same collagenous stroma, the frequent hyalin changes and even calcification are present." In the microscopical sections of the case reported above, the hyaline changes and calcification were similar to those seen in uterine fibroids and bore no relation to the superimposed chronic suppuration.

SUMMARY

Calcification may occur within gastric leiomyomas in the same manner as in uterine fibroids.

A case report of a large calcified gastric leiomyoma, with successful surgical removal, is presented.

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MEDICAL MALPRACTICE*

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THE classic requirements for a plaintiff patient to prove malpractice by the defendant physician are four in number: the doctor had a duty to the patient; he was remiss in fulfilling that duty; as a result of the doctor's negligence the patient sustained an injury; and the injury sustained was a physical injury and not merely the result of the original disease or accident. For mnemonic purposes this has been summarized as duty, dereliction, direct causation and damage. It is beyond the scope of this presentation to explore the defenses against malpractice suits or to discuss the special problems. It is said that 80 per cent of all malpractice claims result from an incautious and usually unjust remark of a subsequent physician treating the patient. Few if any of these actions should have been brought. Too often, a poor result arouses the animosity of the patient, and yet the law says that the physician is not a guarantor of a cure. There are three bulwarks against the unjust suit — good faith, good records and common sense. Good faith implies that the physician treats the patient with tact, conceals no difficulty in diagnosis or in treatment and advises consultation freely. Good records means adequate documentation of physical findings, laboratory reports, progress notes and treatment given — in other words a chronicle of the duration of the physician's care of the patient. Common sense implies that the physician knows the vindictiveness of his patient, the hazard of collection of reluctant fees and the need to assume the expense of treatment of injury to the patient owing to failure of equipment.

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MEDICAL PROGRESS

NEUROLOGY

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THE number of publications in the field of neurology has been unusually large in the past year. Limitations of space make it impossible to discuss more than a small portion of the total number. To summarize the work of the past year for the clinician, an attempt has been made to select articles that have contributed to the understanding of the mode of operation of the nervous system, under the heading of physiology, and those concerned with the application of new forms of treatment, under therapy.

PHYSIOLOGY

Nerve Conduction

There is at present warm interest on many sides in the problem of the physiology of nerve conduction. There are truly almost as many hypotheses or counterhypotheses concerning the nature of the conduction process as there are workers, and contradictory reports are constantly appearing, with the result that the field, although exciting, is confused. The primary controversy at present centers on the question of the relations existing between chemical activities of nerve and the conduction process. Nachmansohn[1] for the past decade has vigorously espoused the hypothesis that acetylcholine constitutes the link between conduction and chemical activity of nerve. He has recently summarized evidence supporting his views.[2] Lorente de Nó, on the other hand, maintains that acetylcholine per se is inert with respect to any influence on neural conduction, and supports the hypothesis that certain quaternary ammonia compounds may constitute the chemical link in the conduction of the nerve impulse. Two statements of his ideas and experimental findings have recently appeared.[3, 4] Von Muralt and his school have been investigating the significance of their observation that a thiamine-like substance is released by nerve coincident with its activity. Von Muralt[5] has particularly emphasized the importance of a correlation of information concerning structural, physical and chemical aspects of nerve activity in the final solution of the problem of nerve transmission,

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and his monograph represents an excellent synthesis of these phases as matters now stand. In an important paper, Huxley[6] has adduced strong evidence for the occurrence in myelinated peripheral nerve of saltatory conduction — that is, transmission of the neural impulse by jumps down successive nodes of Ranvier. It is somewhat difficult to correlate the theories either of Lorente de Nó or of Nachmansohn with this finding, although it may be possible. Indeed, Rosenblueth and his associates,[7] in the course of an experimental and mathematical investigation of the spike potential in nerve preparations that were thought to give single axon potentials, found no evidence for saltatory conduction, and developed an empirical mathematical relation containing 4 parameters to describe the spike potential that does not take cognizance of the nodes of Ranvier.

Motor Cortex

A critical essay by Walsh[8] has clearly shown that affairs at the other end of the nervous system are also in need of further experimental and logical analysis; he has gone into the information and notions concerning the old and fundamental problem of the mode of representation of movement in the cerebral cortex; the two extremes of view in this issue are, on the one hand, the hypothesis that specific muscles are represented in a punctate fashion in the motor cortex, and, on the other, that which maintains that movements are represented locally in the motor area. A related question is whether or not the motor area of the cortex is coextensive with the Betz-cell-bearing portion of the cortex. A statement of the position that there is punctate localization of muscle representation in the motor cortex and that the motor cortex is coextensive with the Betz-cell-bearing area has recently been made by Fulton,[9] one of its leading proponents. Walsh[8] has attacked this general view on anatomic and physiologic grounds.

Electric Activity of Basal Ganglions

The characteristics of the electric activity of the human corpus striatum and neighboring structures in control subjects and in patients with Parkinson's disease and hemiballismus have been studied by Meyers and his colleagues.[10] In 4 of 10 patients with the former disorder, no differences from the controls were found. Nor were any significant differences found between control records and those obtained from a patient with hemiballismus. From among 6 patients with Parkinson's disease, however, 5 were found who exhibited "fast" runs (rate, 17 to 23 per second, duration, 2 to 6 seconds, and amplitude comparable to that of the prevailing waves of the record). Such runs frequently interrupted the slower-frequency phenomena generally characteristic of the subject's record. The sixth case, on the other hand, exhibited a singularly slow rate of dominant waves (5½ per second), whose source appeared to be a well circumscribed region in the dorsal half of the caudate nucleus. The phenomena observed in these 6 cases had no counterpart among the control subjects. It was not possible to identify a consistent relation between the type of electrostriatogram derived from a given subject and the kind and degree of clinical features of Parkinsonism exhibited by him. The findings are interpreted as lending support to the hypothesis that, from the pathophysiologic point of view, Parkinsonism may differ from case to case in regard to the neural loops usurped. A multiordinal concept of the neural mechanism involved in the production of tremors and rigidity is suggested, in contradistinction to a unit-factor process (for example, "disease" of the substantia nigra) such as has traditionally been sought in histopathologic terms.

Spasticity

As Schreiner, Lindsley and Magoun[11] have pointed out, two explanations have been offered for the exaggeration of myotatic reflexes, called spasticity, that follows injury to suppressor systems of the nervous system. These authors have also emphasized that, essentially, both are Jacksonian in derivation: the first considers the spinal stretch reflex to be intrinsically capable of exaggeration when released from suppression; the second attributes reflex enhancement to facilitatory influx from the brain, normally balanced by suppression but exerting an augmented influence in its absence.

Recent investigation has shown that neural discharge arising both in the reticular formation and in the vestibular nuclei of the brain stem, and descending into the cord, can exert a pronounced facilitatory influence upon myotatic reflexes.[11] Schreiner, Lindsley and Magoun[11] have investigated the role of central facilitatory systems in the maintenance of the spastic state by observing the effect of injury to these systems in the brain stem of cats with pre-existing spasticity. They found that lesions of the basal ganglions or upper brain stem did not significantly diminish the spastic state, but frequently led to its increase. The stretch hyperreflexia of spasticity was considerably reduced by transection of the pontobulbar tegmentum and was abolished by additional destruction of the vestibular nuclei. They conclude that spasticity in cats is maintained by facilitatory influx to the spinal cord, conducted by reticulospinal and vestibulospinal tracts.

Alterations of behavior produced in cats by lesions in the brain stem have been reviewed by Bailey.[12] Lesions placed bilaterally in the ventromedian nuclei of the hypothalamus transformed "a normally friendly cat into a vicious snarling beast." Periaqueductal gray-matter destruction produced an akinetic mutism. A lesion in the interpeduncular

nucleus made a normal cat "obstinately progressive" so that he would not turn aside for an obstacle. Lesions bilaterally just above and posterior to the mamillary bodies induced catalepsy. Bailey interprets these experiments as meaning that the brain stem "does more for behavior than merely transmit impulses to and from the cerebral cortex."

Electromyography

In an extensive review of the fundamental principles of electromyography, Denny-Brown[13] warns of the limitations that must be set upon interpretation of results of this procedure when it is used diagnostically. He points out that few types of changes are specific for the various classes of nervous disorder. He urges that, when the method is used as an indicator of neuronal activity in pathologic processes, it be controlled by critical appraisal of the mechanical contractile activity in the muscle under observation, since the electric manifestations of activity of motor units may be widespread, growing wider in proportion to the intensity of discharge. He believes, however, that myography has valuable clinical uses that can be expanded by further research.

Using methods permitting precise timing of events to a fraction of a millisecond, Kugelberg and his associates[14] have investigated the form and duration of the action potential in normal human muscle, and applied their findings in this study to the electromyographic differentiation of primary muscle disease from chronic disorders of the lower motor neuron.[15] Their evidence indicates that, among other differences, the action potentials of muscles with primary disease have a shorter average duration than those of normal muscles, whereas the muscles supplied by diseased motor neurons have, on the average, action potentials of longer duration than the normal.

Cerebral Circulation

The nitrous oxide procedure for measuring cerebral blood flow (CBF), introduced by Kety and Schmidt[16] has recently been employed by a number of investigators. A report on normal values of blood flow, oxygen utilization and glucose utilization obtained by this method has now appeared from an additional laboratory, and a comparison of values found in the different laboratories by this procedure reveals variations that are of importance in evaluation of results obtained by the method. Sheinberg and Stead[17] at Duke University find that CBF in normal male subjects measured by the nitrous oxide method varies from 50 to 103 cc. per minute per 100 gm. of brain. This mean figure for CBF, with subjects supine, is 65 cc. per minute per 100 gm. (standard error, 2.1) — a significant difference statistically from a mean of 54 (standard error, 2.1) reported by Kety. The reasons for this difference are not clear. Variations in the average age of the subjects or difference in the over-all technic of the two laboratories may be responsible, Sheinberg and Stead state. They observed cerebral arteriovenous oxygen differences, with subjects supine, to vary from 4.4 to 7.6 vol. per cent, with a mean of 6.02, compared with a mean reported by Kety of 6.3. The mean figure for cerebral oxygen utilization obtained at Duke University was 3.8 cc. of oxygen per minute per 100 gm. of brain, whereas that found in Kety's laboratory was 3.3 cc. (a difference attributable to the discrepancies in values of cerebral blood flow obtained in the respective laboratories). Cerebral arteriovenous glucose differences (with subjects supine) ranged from 6 to 16 mg. per 100 cc., and the cerebral glucose utilizations varied from 3.9 to 9.5 gm. of glucose per 100 gm. of brain per minute. The ratio of cerebral arteriovenous glucose difference to cerebral arteriovenous oxygen difference ranged from 1.10 to 2.46, with a mean of 1.67. The rather wide range of values is attributed primarily to the method of glucose determination used. The ratio to be anticipated from the chemical equation of the complete breakdown of glucose to carbon dioxide and water is 1.34. The authors speculate about whether this deviation from the calculated value may not be a reflection of the occurrence of partial oxidation of glucose to pyruvic and lactic acids, and the conversion of carbohydrate to fat.

Observations made by Sheinberg and Stead[17] indicate that there is a decrease in CBF with subjects in the erect position, but that the cerebral oxygen arteriovenous difference increases, thus making for a relatively stable rate of oxygen consumption by brain in the two positions. They also estimate that approximately 14 per cent of total cardiac output goes to brain in the resting state, whereas 22 per cent of the total oxygen consumption of the body is by brain.

The nitrous oxide method has been used to study the effect of bilateral stellate ganglion block on the cerebral circulation of normotensive and hypertensive persons (and in 2 with Parkinson's disease) by Harmel and his collaborators.[18] This group finds that stellate block induces no significant alteration in CBF or "cerebral vascular resistance" — mean arterial tension divided by CBF — in any of their subjects. These findings make it somewhat difficult to understand the mechanism whereby block of the cervical sympathetic trunk produces an improvement in patients with apoplexy, as reported by Gilbert and de Takats.[19]

Also employing the nitrous oxide method, Shenkin and Yaskin[20] investigated CBF in a series of patients with post-encephalitic Parkinson's disease. They found cerebral flow decreased when measured by this procedure. These authors attribute the decrease in CBF to an increase in CVR ("cerebrovascular resistance"), which in turn they consider to be the result of vascular spasm, since they found

that bilateral stellectomy in several of their patients increased CBF and reduced CVR. Cerebral oxygen consumption was also stated to be below levels (Kety normals, presumably) in these patients, and bilateral stellate ganglionectomy was not clearly proved to affect it. These investigators conclude that their findings point to a vascular component in the pathology of postencephalitic Parkinson's disease. They believe that the progressive features of this disease, after subsidence of the acute inflammatory phases, may be the result of progressive vascular occlusion after initial vascular damage.

Gardner and Williams[21] have reported on the clinical effects of bilateral resection of the superior cervical ganglion in 34 patients with a Parkinsonian syndrome, some of whom (exact number unstated) had the postencephalitic type. No objective improvement was noted after the operation, but in several cases a favorable response in mood was observed.

Therapy

Mephenesin (Myanesin)

Increased muscular tone and tremor are symptoms of neurologic disease constantly demanding therapy. In the past, curare and its congeners and various belladonna derivatives have been particularly investigated regarding their usefulness in the treatment of these symptoms. A compound that apparently represents a different pharmacologic and neurophysiologic approach to the treatment of spasticity, rigidity and tremor is Mephenesin (Myanesin), 3- (2′methylphenoxyl) propane-1,2-diol, which has been the subject of numerous pharmacologic and clinical studies in the past few years. This drug is commercially available under various names (Lissephen, Oranixon, Tolserol and Toloxynin in the United States, Myanesin in Great Britain and the British Commonwealth, Relaxar in France, and Glycresin in Northern Europe). At very high concentrations, it has a curare-like action, in that it abolishes indirect stimulation of muscle through nerve at a time when direct stimulation still produces muscular contraction; however, in the dosages in which it is employed in patients, no such curare-like effect is observed. Several investigators have noted that small, nonparalyzing doses do not affect the stretch reflex (or two-neuron arc), but do depress or abolish crossed extensor reflexes, which are believed to depend on internuncials for their mediation. Thus, it is suggested that Mephenesin has a selective depressant effect on internuncial neurons of the spinal cord.[22]

Furthermore, studies in cats have shown that in nonparalyzing doses the drug depresses or counteracts both facilitatory and inhibitory extrapyramidal systems.[22] On the basis of these animal experiments it appears that it decreases spasticity by reducing chronic extrapyramidal facilitation of stretch reflexes. Since facilitation dominates inhibition in the spastic state, mechanisms subserving it are presumably more affected by the drug.

Berger[22] points out that Mephenesin possesses a powerful antagonistic action to the effects of strychnine and suggests that it may be an agent of considerable value in the treatment of strychnine poisoning. This versatile drug also has antipyretic, analgesic, antibacterial and local anesthetic action.[22]

Mephenesin has been given a trial in the treatment of a number of nervous diseases. Gammon and Churchill[23] found that, administered orally, it is effective in certain cases of paralysis agitans, diminishing both rigidity and tremor in about 50 per cent of patients. It is stated to be of value in suppressing or diminishing athetotic and chorea-like movements in patients with cerebral palsy and in those with bilateral athetosis and dystonia musculorum deformans. Contradictory reports have appeared on its effect on tremor in multiple sclerosis. Gammon and Churchill[23] have observed an increase in intention tremor in 2 patients with this disease. Berger noted a favorable effect on intention tremor of arms and legs and in head wagging in 3 out of 19 patients with multiple sclerosis.

Berger and Schwartz[24] have stated that after oral administration some hemiplegic patients show a decrease in spasticity, with recovery of some voluntary movement.

Quite a number of reports have stated that Mephenesin given intramuscularly or intravenously is of considerable value in the treatment of tetanus.[25-29]

Hunter and Waterfall[30] have tried the effect of the drug in 3 patients with continuous epileptic attacks and observed immediate disappearance of the seizures, after intravenous doses of 0.4–1.0 gm. Schlesinger[31] also found it of value in status epilepticus. Gammon and Churchill[23] observed the disappearance of the characteristic spike and dome wave pattern in the electroencephalograms of 6 patients with petit mal.

Mephenesin has also found use in psychiatric therapy. Schlan and Unna[32] reported that in patients with anxiety states, it alleviates anxiety without clouding consciousness. They also report that the drug has a sedative effect in manic depressive psychoses. Schizophrenic patients showed a sedative reaction only when their environment was not disturbing. Gammon and Churchill[23] observed improvement in a patient with a reactive depression; a deteriorated negativistic schizophrenic patient became communicative, and an agitated patient became calm and communicative.

Mephenesin is apt to produce hemolysis and hemoglobinuria as well as kidney damage and anuria after intravenous injection.[22] These toxic effects have not been observed after oral administration, however.[22] Simultaneous failure of circulation and respiration of central origin after intravenous in-

jection of 3 gm. has also been reported by Hunter.[33] This was reversed by 5 cc. of nikethamide.

Panparnit

Among other new drugs of value in the treatment of hyperkinetic and dystonic conditions is caramiphen hydrochloride (Panparnit), the diethylamino ethyl ester of phenylcyclopentanecarbonic acid. Schwab and Leigh[34] found that the drug was superior to previous medication in 65 per cent of 50 patients with Parkinson's disease. Dunham and Edwards[35] also observed some improvement in 9 out of 19 patients suffering from paralysis agitans. Dryness of the mouth and blurred vision are stated to be of lesser severity after Panparnit than after atropine. Sciarra, Carter and Merritt[36] did not find Panparnit to be superior to the belladonna drugs in the treatment of patients with Parkinsonian rigidity or tremor.

Trihexyphenidyl

Corbin[37] and Mackay[38] have stated that Mephenesin has been of no value in their experience in the treatment of Parkinson's disease, and Corbin[37] has claimed that Artane, or trihexyphenidyl(3-[1-piperidyl]-1-phenyl-1-cyclohexyl-1-propanol hydrochloride), is more effective than Panparnit in the treatment of extrapyramidal diseases. Doshay and Constable[39] have also reported Artane to be of use in the treatment of Parkinson's disease.

This drug is claimed to be relatively free of side effects and to produce a beneficial psychologic response, and to diminish rigidity. Corbin[37] emphasizes the fact that all the available methods of treating extrapyramidal diseases are palliative, and stresses the necessity of adapting therapy to the patient, rather than standardizing it.

ACTH

Although interest in the effect of thymectomy and anticholinesterases on the symptoms of patients with myasthenia gravis continues,[40, 41] attention also is turning to the influence of adrenocorticotrophic hormone (ACTH) on this disease. Among the many reasons for concern with the nature of the effect of ACTH on myasthenia gravis is the report that the hormone increases acetylcholine (ACh) synthesis in vivo.[42] Evidence has also been adduced that the immediate cause of the symptoms of myasthenia gravis is the decrease in ACh synthesis.[43] Furthermore, the administration of ACTH results in a decrease in mass of the thymus,[44] surgical removal of which has been reported to induce remissions of the disease,[45] and which is said to contain a fraction that inhibits the synthesis of ACh.[46] Torda and Wolff[47] administered ACTH to 5 women moderately to severely ill with myasthenia gravis and to a control group also consisting of women. They attempted to evaluate objectively by myography and electromyography the response of neuromuscular function and studied the influence of the blood serum of those receiving the hormone on ACh synthesis in a test system. During the period of administration of the hormone, the patients are said to have experienced an increase in disability. The second day after completion of a series of injections all patients experienced changes suggesting the beginning of an incomplete remission in their disorder. These changes consisted of marked improvement of muscle function at a time when the patients were on reduced Neostigmine medication. The much reduced ability of the blood serum to support ACh synthesis returned to normal, and the myogram and electromyogram became similar to those of healthy people. The improvement noted persisted during the three months' period following ACTH administration covered by the report of Torda and Wolff.

During the period of administration of the hormone there was an increase in the symptoms, which according to Torda and Wolff may be the result of the changes in many phases of metabolism known to be produced by the ACTH; several of the metabolic changes induced by this hormone have been shown to impede the synthesis of ACh and augment the symptoms of patients with myasthenia gravis. Thus, administration of ACTH has been reported as resulting in a drop in reduced blood glutathione[48]; experimental increase in reduced blood glutathione, Torda and Wolff say, ameliorates symptoms, and they imply, although on this point there does not appear to be any direct evidence, that a drop in reduced blood glutathione will result in an aggravation of the myasthenic syndrome.

Soffer and his colleagues[44] have reported their experiences in the administration of ACTH to a woman with myasthenia gravis. This patient had a rather large mass in the anterior mediastinum that was demonstrable on x-ray examination and thought to be an enlarged thymus. After administration of 40 mg. of the hormone daily in four divided doses for four days, there was a decided shrinkage of the mediastinal mass. About two weeks after cessation of therapy, the mass in the mediastinum began to swell, reaching its original size within another week. During the period of treatment Soffer et al. observed no change in the patient's symptoms and no decrease in daily Neostigmine requirements. Three or four days after therapy had been discontinued, the patient began to feel better, the daily need for Neostigmine became progressively less, and within two weeks after cessation of therapy no Neostigmine was required. The ability to do without Neostigmine continued up to thirty-six days after the conclusion of therapy, at which time the report was made. It should be noted that clinical improvement continued and was maintained, despite resumption of the original size of the mediastinal mass.

Hellman[49] has reported briefly that administration of ACTH produced an augmentation of symptoms in patients with myasthenia gravis, similar to that described by Torda and Wolff, but in his patients, as far as one can tell from his short report, no remission of symptoms was noted after therapy was stopped.

Vitamin B_{12}

The attempt to isolate the active factor or factors in liver that are curative of the various manifestations of pernicious anemia resulted in the discovery of pteroyl glutamic acid in 1945 and of vitamin B_{12} in 1948. Clinical observations have shown that pteroyl glutamic acid does not completely replace potent extracts of liver in the treatment of this disease.[50] The appearance or progression of clinical signs of nervous-system involvement, and indeed hematologic relapse, may take place during therapy with this agent.[51] However, the results of clinical trials with vitamin B_{12} seem to indicate that this substance does not have the therapeutic limitations of pteryol glutamic acid, and it seems to be as effective as liver extract in the treatment of all the manifestations of pernicious anemia.[52]

Hall, Krusen and Woltman[53] treated 12 patients with involvement of the nervous system associated with pernicious anemia by means of parenterally administered vitamin B_{12}, conjointly with co-ordination exercises. Signs and symptoms of neurologic involvement, such as paresthesias, ataxia, disturbed vibratory and position sense, either disappeared or showed improvement, in all 12 patients. Ten micrograms of vitamin B_{12} was injected intramuscularly daily, or every second day, for three to six months. Maintenance doses of from 10 to 20 microgm. were given intramuscularly, once each week, thereafter. Although these amounts of vitamin are in excess of those needed by patients with pernicious anemia without involvement of the nervous system, these investigators suggest not only that this high dosage is necessary but also that even larger doses than these may be needed for increased effectiveness in control of nervous-system manifestations of the disease. They also believe that co-ordination exercises make a definite contribution to the improvement of their patients. Also stressed in this report is the importance of institution of intensive therapy, early in the course of nervous-system involvement, before axis cylinders are destroyed, an irreversible event. No untoward reactions to therapy were reported in these patients. Hematologic control was apparently good, and the appearance of lingual signs on vitamin B_{12} therapy is not reported. At the time of the writing of this review, reports on the effects of vitamin B_{12} on the mental symptoms, present in some patients with pernicious anemia and ranging from mild personality disturbances to frank psychoses, are not available. Nevertheless, the fact that vitamin B_{12} seems to provide prompt and adequate therapy for all other abnormalities that accompany the disease no doubt supports the conclusion that pernicious anemia is the result of a "single type of metabolic defect or deficiency."[50-52]

Antibiotics

In general, those who have recently described their work with chemotherapeutic agents in the treatment of nervous-system infections are still emphasizing the value of early bacteriologic diagnosis, with prompt institution of appropriate therapy; prolongation of therapy for some time after clinical and bacteriologic recovery; the use of several therapeutic agents in patients seriously ill, or in those infected with bacterial strains resistant to the usual drug of choice; the maintenance of nutrition and fluid balance; extreme caution in the use of intrathecal therapy (if it is used at all), as well as alertness to the toxic effects peculiar to the various drugs; and the importance of ascertaining and treating the primary focus of the bacterial infection.

In Keefer's[54] series of 5000 patients with bacterial meningitis the most common cause was the meningococcus. The efficacy of sulfadiazine in meningococcal meningitis has been re-emphasized by Page and Page.[55] Treatment of 60 consecutive patients with this disease at an Army station hospital (in 48 the diagnosis was proved bacteriologically) with sulfadiazine resulted in recovery in all patients. The therapeutic procedure followed in this series may be outlined as follows: immediately after the lumbar puncture, 1000 cc. of one-sixth molar solution of sodium lactate was administered intravenously, and then 5 gm. of sodium sulfadiazine was given, the latter operation being performed without removal of the original needle, if possible. The entire procedure was repeated in eight hours if the patient was unable to retain oral medication. The authors recommend a blood level of 10 to 12 mg. of sulfadiazine per 100 cc. until the temperature has returned to normal, and blood levels of 5 to 8 mg. per 100 cc. for another five to seven days thereafter. If the patient is able to retain oral medication, administration of 16 gm. of sodium bicarbonate in divided doses of 4 gm. each is recommended in place of intravenous lactate. Sodium bicarbonate is continued for at least forty-eight hours after discontinuance of the sulfadiazine. The patients received an average total dosage of 7.75 gm. of sulfadiazine intravenously and 49 gm. orally during a period of treatment averaging ten and two-tenths days. The authors also recommend a daily fluid intake of 3500 cc. and an output of 1200 cc. Maintenance of alkaline urine and adequate urine output minimized renal complications in their series.

Sulfadiazine alone or in conjunction with penicillin is recommended for the treatment of streptococcal meningitis,[56] and penicillin is considered the best agent against staphylococcal meningitis,[56] although, of course, combinations of therapeutic agents may be advisable in very severe illnesses or in the presence of extremely resistant bacterial strains.

The tubercle bacillus is second in frequency as an infective agent in meningitis, according to Keefer's report. This disease, of course, was usually fatal until the advent of streptomycin. During the last several years isolated cases or small series of apparent cures of this disease by treatment with streptomycin have been reported. In the past year several rather large series of patients treated with this antibiotic have been described. Cairns and Taylor[57] treated 48 patients with tuberculous meningitis in the Radcliffe Infirmary at Oxford. All but 1 of these cases were bacteriologically or histologically verified. Twenty of the 48 patients survived. Of these, 19 had completed the course of treatment at the time of the report. Out of the 19, 18 were well and free from symptoms, apart from deafness and vestibular disturbances. The other patient was severely demented after two hundred and seventeen days of illness, but was showing some improvement. The Oxford workers stress the fact that the details of therapy of tuberculous meningitis with streptomycin in the present state of development must be regarded as tentative. They state that intrathecal therapy with streptomycin must be combined with intramuscular therapy at least for the first month, if not longer. They consider the chief causes of failure of therapy to be delay in the start of treatment and the stopping of it too soon. They emphasize that daily intrathecal injections of streptomycin often present a formidable problem, particularly in infants and young children. They are careful to point out the complications and dangers attendant upon repeated lumbar punctures and the injection of streptomycin into the subarachnoid space. They also believe, on the basis of their experience, that it is justifiable to take active steps to remove foci of tuberculous infection surgically as soon as acute symptoms of meningitis can be controlled. Choremis and his co-workers,[58] in the Pediatrics Clinic at the University of Athens, Greece, have treated 63 patients with tuberculous meningitis, 29 of whom survived. This group also employs combined intramuscular and intrathecal injections of streptomycin. They warn that if the patient begins vomiting, develops a rapid pulse and shows signs of respiratory disturbance and slowly developing opisthotonos, cessation of both intramuscular and intrathecal streptomycin therapy is indicated. If after several days of rest from streptomycin therapy these symptoms subside, streptomycin administration may be gradually resumed. The therapeutic procedures employed by this group differ from those of the Oxford investigators in several respects. First of all, Choremis et al.[58] employ rest periods in the administration of streptomycin, the first period of rest being from a month to six weeks after the beginning of treatment; Cairns and Taylor[57] used continuous treatment. Secondly, the Athens group employs tuberculin as adjuvant therapy whereas the Oxford workers do not. And, thirdly, Choremis employs smaller doses than Cairns and Taylor do. Daniel[59] has pointed out that so far as the gross morbid anatomy of the central nervous system in cases of tuberculous meningitis treated with streptomycin is concerned, the main pathological differences between untreated cases of tuberculous meningitis and those treated with streptomycin coming to autopsy are due, as far as one can see, to the prolongation of the healing response to the disease. The presence of a greenish-yellow, often gelatinous, exudate at the base of the brain has been regarded as a characteristic feature of tuberculous meningitis. Daniel, in studying streptomycin-treated cases, has come to regard the basal midbrain exudate as being of importance in two respects: because of its interference with the circulation of the cerebrospinal fluid and because of its malign influence upon the blood vessels and especially the arteries that it surrounds. Extension of this basilar exudate may involve the origins of all the major cerebral arteries and also their small branches. In cases in which life has been considerably prolonged by streptomycin treatment, the basal exudate is usually thicker than in the untreated fatal cases, and instead of being gelatinous it is of a wooden-hard consistence. Arteries imbedded in tuberculous exudate commonly develop an arteritis, with consequent diminution or even obliteration of their lumens. This arteritis of proximal parts of the main cerebral arteries and their branches is one of the most serious and fatal concomitants of the basal exudate. The result of the arteritis is at best some degree of anoxia and at worst actual infarction of the area supplied by the affected vessel. The author presents cases of patients in whom the exudate has involved small vessels supplying the midbrain with a collar of exudate, leading to infarction of the area nourished by that vessel. In other patients there is a shrinkage of the whole of a frontal lobe as the result of infarction of the basal ganglions, owing to arteritis of branches or the cerebral arteries. Tuberculous encephalitis is often seen in the depths of the sulci of both cerebral and cerebellar hemispheres; in some cases of long standing many small foci of cortical necrosis may be seen. In others, small or large tuberculous granulomas in all stages of activity and healing are found in the depths of the sulci. These are usually invisible on the surface and are seen only when the brain is cut. It is reasonable to suppose that these may well be the foci

from which reinfection occurs in some of the cases in which relapse takes place. The clinical finding indicating that early diagnosis is vital if complete cure of tuberculous meningitis is to be achieved finds its pathological background in the desirability of achieving diminished formation of basal exudate.

The management of pneumococcal meningitis has been reviewed by Waring and Weinstein.[60] The pneumococcus is the third most frequent cause of purulent meningitis in Keefer's[54] series. This organism can find its way into the meninges by several different routes. In a series of 409 patients, the authors found that the meningeal infection resulted from extension in the ear or mastoid in 151, as a primary disease in 122, after pneumonia in 101 and from skull fracture in 19 patients. Sinusitis was the original infection in 13 patients and it occurred in 3 after cranial operations. The authors point out that, although in about a fourth of the patients pneumococcal meningitis occurred in patients with a pre-existing pneumococcal pulmonary infection, meningitis is actually uncommon as a complication of pneumonia, the incidence varying between 0.4 and 1.9 per cent. Pneumococcal meningitis may occur at any age but is relatively more frequent in the younger and older age groups. The disease was almost uniformly fatal before the advent of chemotherapy, but with combined penicillin and sulfonamide therapy, the authors state that a survival rate of 60 to 70 per cent may be expected, the recovery rate being perhaps lower in infants, in the aged and in patients with pneumonia, and perhaps higher in adult patients treated early. Regarding therapy the author recommends intramuscular and intrathecal administration of penicillin, sufficient sulfadiazine to maintain a blood level of 15 mg. of free drug per 100 cc. and continuance of full therapy for about eight to ten days after the spinal fluid is sterile. Penicillin and sulfadiazine are gradually eliminated from the therapeutic regime. They believe that surgical attack on infected foci should be delayed until marked improvement either has occurred or is demonstrated to be unlikely as a result of antibiotic therapy. These authors state that sequelae involving various parts of the nervous system may be expected, particularly in infants. Brain abscess and endocarditis were not common in their series, but when present reduced the chance of survival, although 2 patients in this group with probable endocarditis survived.

In Keefer's[54] series *Haemophilus influenzae* was the fifth most common cause of meningitis. Until recently this form of meningitis was usually fatal. Smythe,[61] in treating 11 patients affected with this organism by streptomycin, reports 8 recoveries. Among the 3 deaths was 1 patient whose infecting organism developed resistance to streptomycin as shown by in vitro tests. He believes that streptomycin gave good results in the mild or moderately severe cases but was unsatisfactory in 3 very severe cases. In view of the failure of streptomycin in severe cases and the possible development of resistance and of resistant strains, Smythe suggests that all cases of meningitis due to *H. influenzae* be treated with streptomycin and sulfonamides; in severe cases either antiserum or penicillin should be given in addition. In treatment he gave 20 mg. of streptomycin per pound of body weight daily, divided into six intramuscular injections. He also gave a daily intrathecal injection of 25 to 100 mg. in 5 cc. of saline solution, the dose varying with the age of the patient and the severity of the disease. Treatment by both routes was continued until the cerebrospinal fluid had been sterile for at least a week. No other specific treatment was given unless there was no response to streptomycin. Blood transfusions were given when anemia was present. He reports no reactions from intrathecal injections.

A rare, but usually fatal, cause of meningitis is *Klebsiella pneumoniae* (Friedländer's bacillus). Ayvazian[62] has described a patient with this condition who was successfully treated with streptomycin and sulfadiazine; he considered the former agent to have been the effective one. He also mentions the rather frequent association of infections with this bacillus and the presence of diabetes.

Herman[63] has recounted his experiences with typhus fever during the Warsaw epidemic of 1941-42. Recalling the epidemic of 1918–20, he writes that during that period few patients displayed signs of neural manifestations, but that many gangrenous complications were observed, whereas in the recent epidemic, the reverse was true. The nervous-system involvement is widespread in this infection, and may involve almost any part of the central nervous system, its coverings or the peripheral nerves. This possibility of widespread involvement is reflected in the diverse clinical findings encountered, ranging from signs of meningeal irritation, increased intracranial pressure, extrapyramidal, pyramidal and cerebellar signs and epileptic manifestations to involvement of the cranial and peripheral nerves. Among the new antibiotics, chloramphenicol (Chloromycetin) and aureomycin give great promise of an effective treatment of this and other rickettsial infections.[64]

Torulosis, or cryptococcosis, is another rare disease of the nervous system; approximately 100 cases have been reported.[65] It is the result of infection of the nervous system by *Torula histolytica* (*Cryptococcus hominis*) — spherical, yeast-like fungi that reproduce by budding. These organisms are widespread in milk and other foodstuffs and have been found in the mouth and on the skin of healthy people. Conditions of pathogenicity for man are not known; any tissue may become invaded, but the pulmonary and nervous systems are apparently most often infected. Daniel, Schiller and Vollum[65] remarked that the presenting clinical picture of

central-nervous-system involvement may be confusingly similar to that of tuberculosis. In general, two forms of the disease seem to occur, one being a diffuse meningoencephalitic type and the other, less common form, a circumscribed, granulomatous mass in the brain.[66] Symptoms can include severe headaches, occasional epileptic manifestations, papilledema, cranial-nerve palsies and pyramidal or cerebellar signs. Examination of the spinal fluid may reveal the torula, — which can be mistaken for lymphocytes, of course, — but the organism may not be seen; hence it may be impossible to prove its presence, except by culture.[65] The organism does not seem to be sensitive to penicillin or streptomycin, but apparently is to sulfathiazole and gentian violet.[66]

Daniel et al.[65] state that surgical removal of the granulomatous masses can be successfully performed, without spreading the organisms through the subarachnoid space and with some clinical success. Antibodies to the organisms are not produced, apparently, and there are no immunologic aids at present to the diagnosis.

Cysticercosis cerebri is only occasionally seen in the United States, but is rather common in certain areas of the world. Stepien and Chorobski,[67] at the Warsaw Neurological Clinic, have seen 23 cases personally and have collected 71 from the literature. The results of invasion of the brain by this parasite include signs and symptoms of an expanding focal lesion, psychologic disturbances and internal hydrocephalus. The authors recommend excision of the cyst that produces the first two classes of symptoms, whereas when hydrocephalus is present (usually produced by a cyst at the base of the brain) they advise one of the palliative procedures available for relief of this condition.

Anticonvulsants

Although treatment of the patient with a convulsive disorder has many aspects, the most important of these is the use of anticonvulsant drugs. Merritt[68] has discussed the proper use of the standard anticonvulsants, emphasizing that they cannot be employed routinely but must be fitted to the patient. He points out, however, that certain generalizations can be made about the drug most likely effective in the various clinical types of seizures. Thus, phenytoin sodium (Dilantin) and phenobarbital are the most efficacious drugs in the treatment of patients with grand-mal seizures. After initial therapy with one or the other, if it proves ineffective, or is not tolerated, the other can be substituted, or they can be used in combination. Occasionally, Mesantoin (3-methyl-5,5 phenyl hydantoin) or combinations of this drug with phenytoin sodium will give best results. Rarely, bromides or a combination of bromides and phenobarbital or phenytoin sodium will be most effective. Merritt emphasizes the fact that the change from one drug to another, in the treatment of any clinical type of epilepsy, should not be abrupt, or else status epilepticus may occur. Full dosage of the original medication should be continued for several days after initiation of therapy with a new compound, until an adequate reservoir has been obtained in the patient's body.

Gibbs, Everett and Richards[69] have reported that Phenurone (phenylacetylurea) is particularly effective against psychomotor seizures. Of 58 patients with psychomotor epilepsy, half were reported to be improved greatly. Patients with grand-mal and petit-mal epilepsy were also described as being greatly improved (a third of the patients with the former and about half the patients with the latter). The minimum effective dose of Phenurone is reported to be 1.5 gm. daily, the average dose 2.5 gm., and the maximum dose 5 gm. Particularly interesting in the experience of these investigators with the drug is their finding that personality disturbances in patients with psychomotor epilepsy were usually exaggerated. This usually occurred only if the psychomotor seizures were controlled, although in a few cases personality disturbances flared up even though seizures continued. The maintenance of a few patients with psychomotor epilepsy in a seizure-free condition was considered undesirable, because severe psychiatric symptomatology developed whenever seizures were controlled. On withdrawal of Phenurone, seizures usually recurred promptly, and personality disorders subsided forthwith. In 1 patient whose seizures were checked with Phenurone, a severe psychotic state subsequently developed with auditory hallucinations and delusions of persecution; on discontinuance of Phenurone, seizures did not recur. Electroshock therapy was given to this patient without improvement in mental status, but with reappearance of seizures; however, insulin-shock therapy succeeded in removing most of the manifestations of the mental disorders.

Gibbs et al.[69] state that toxic symptoms with Phenurone include skin rashes, jaundice, kidney effects and insomnia. They warn that one must be on guard against the possibility of damage to the blood-forming system.

The problems of post-traumatic epilepsy have been surveyed by Walker,[70] with particular reference to his experience with approximately 250 patients at the post-traumatic epilepsy center at Cushing General Hospital. The frequency of convulsive seizures following brain trauma is difficult to assess, Walker states, but is apparently directly related to the severity of the cerebral injury. In a survey of cases from World War II, approximately 10.8 per cent of patients with cerebral trauma had seizures. Of patients with penetrating head injuries, 14.9 per cent experienced convulsions. This compares with a seizure incidence of around 45 per cent in similar casualties from World War I. Walker

attributes the low incidence of seizures in this series to careful débridements and a relative freedom of the wounds from infection. In the experience of the group at Cushing General Hospital the treatment of post-traumatic epilepsy was found to be satisfactorily taken care of in the main by medical means. Operation, Walker suggests, is indicated only for repair of surgical lesions, such as skull defects, or in the event that medical management is ineffective in controlling convulsive seizures. Walker removes the epileptogenic focus and scar by incision all the way through to the ventricle, by removal of the focus and the scar down to normal white matter or by subpial resection of the focus. The epileptogenic focus is usually at the margin of the cerebral scar, and Walker employs Metrazol and electrically induced, as well as spontaneous, electric activity of the cortex in localizing the epileptogenic focus. In addition to the primary focus, which may be shifting, secondary foci may develop, either on the same side or on the side opposite the injury. Anticonvulsant drug therapy is continued at a preoperative level for two years after the operation. If no further attacks occur after two years, the medication is decreased and gradually eliminated over another two-year period. If seizures still occur after surgical intervention, further efforts are made to control the epilepsy medically.

Among 238 patients with post-traumatic epilepsy handled at Cushing General Hospital, 130 were discharged as controlled by medical therapy, 42 were considered to have had inadequate hospitalization, and 66 were not controlled medically. Out of 36 patients operated on after failure of medical therapy, 17 still had major attacks, 12 had no attacks, and 7 had either an aura or one attack in the course of the first postoperative year. This is to be compared with a control group of 20 patients with post-traumatic epilepsy uncontrolled by medication and not operated on, of whom 17 still had major attacks, 1 was free of attacks, and 2 had had one aura or one attack during the control period.

The appearance of a cerebral dysrhythmia in relation to large doses of potassium chloride administered in the treatment of Ménière's syndrome has been described in a forty-seven-year-old man by Brown.[71] In addition to electroencephalographic changes present while the patient was receiving large doses of potassium chloride, he had episodes in which he suddenly fell to the ground.

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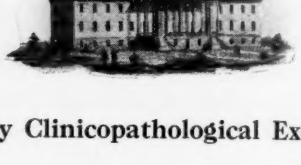
CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 36371

PRESENTATION OF CASE

First admission. A fifty-four-year-old woman entered the hospital complaining of painful, swollen joints of three months' duration.

Thirty-eight years previously, at the age of sixteen, the patient injured the right knee. Subsequently she had attacks of pain, swelling and warmth in this joint occurring every two or three years. At the age of twenty-three there was a one-year episode of low-back pain radiating into both hips for which the patient took large doses of aspirin. Fourteen years prior to admission at the age of forty she began to have pain and swelling of first the distal and then the proximal interphalangeal joints. These attacks lasted one or two weeks, occurred about ten times a year, were more frequent in cold, damp weather and resulted in permanent deformity and limitation of motion of the fingers. Three years before entry she began to have a hacking, nonproductive cough, which was occasionally severe enough to produce vomiting. She became very weak and anorexic and over the next three years lost 80 pounds of weight. One year after the cough began she was studied at another hospital, where she was found to have a temperature of 101°F., a hemoglobin of 8.2 gm. per 100 cc., a red-cell count of 2,500,000 and a total protein of 5.6 gm. per 100 cc. A stool was guaiac positive. Gastric analysis yielded no free acid. Bone-marrow biopsy was negative. A gastrointestinal series showed hypertrophic gastritis and a barium-enema examination was negative. X-ray films of the chest showed bilaterally enlarged hilar nodes, which did not change in size following a trial of deep x-ray therapy, although the cough improved. The patient was discharged after receiving three blood transfusions. In the following months she received a course of liver injections, iron pills, intramuscular gold injections and a short course of vitamin D therapy and had complete dental extractions, with no improvement in either the anemia or the joint pains. Six months before admission she went to Florida for the winter, only to find that the damp, cool weather aggravated the arthritis and that the cough returned. Four months before entry, following a three-day episode of fever (maximum temperature of 102°F.), a physician prescribed vitamin D, 300,000 units daily by mouth, which the patient took for approximately two and a half months. She habitually drank 3 to 5 glasses of milk a day; but during this period was so incapacitated that she confined her diet to

3 quarts of milk a day. Shortly thereafter she began to notice soft, tender, evanescent swellings around the shoulders, wrists, elbows, fingers, back and legs and for two weeks prior to admission had been confined to bed because of them. Urinary symptoms of any sort were denied. For three months prior to admission there had been severe generalized pruritus.

Physical examination revealed a pale, dry-skinned, tremulous woman appearing much older than her stated age. Band keratitis was noted in both eyes. The lungs were clear to percussion and auscultation, but there was a hacking, nonproductive cough. A Grade II systolic murmur was heard over the precordium. The abdomen was normal. Numerous soft, freely movable, fluctuant, slightly tender masses, 1 to 7 cm. in diameter, were felt in the periosteal or periarticular tissues in the right thumb, right radial tuberosity, left ulnar tuberosity, right posterior scapulohumeral joint, lower border of the left scapula and left sacroiliac area. The skin over these masses was neither hot nor discolored. There were both degenerative and rheumatoid changes in the joints of the fingers, wrists, knees and feet.

The temperature was 102°F., the pulse 100, and the respirations 25. The blood pressure was 100 systolic, 60 diastolic.

Repeated urinalyses showed a maximum specific gravity of 1.006, a ++ test for albumin, occasional granular casts and a ++ Sulkowitch test. A urine concentration test showed a maximum specific gravity of 1.010. The phenolsulfonphthalein excretion was less than 15 per cent in two hours, and the urea clearance was 7 per cent of normal. Examination of the blood disclosed 7.5 gm. per 100 cc. of hemoglobin, 2,530,000 normochromic, normocytic red cells and 9600 white cells, with 76 per cent neutrophils, 16 per cent lymphocytes, 5 per cent monocytes and 3 per cent eosinophils. The sedimentation rate was 1.4 mm. per minute, with a hematocrit of 52.5 per cent. The mean corpuscular volume was 83.3 cubic microns, the mean corpuscular hemoglobin 23.3 micromicrogm., and the mean corpuscular hemoglobin concentration 28 per cent. A sternal-marrow biopsy was characteristic of simple chronic anemia. Repeated stool examinations were negative for blood, ova and parasites. Gastric aspirations yielded no free acid and only a trace of combined acid before and after histamine. The nonprotein nitrogen was 62 mg., and the total protein 6.24 gm. per 100 cc., with an albumin-globulin ratio of 2.22; the calcium was 13.4 mg., the phosphorus 5.7 mg., the alkaline phosphatase 5.9 units, and the blood uric acid 7.1 mg. per 100 cc. The twenty-four-hour urinary calcium excretion on admission was 125 mg. The blood Hinton test was negative. A tuberculin test was positive in a dilution of 1:10,000. Abundant Type 13 pneumococci were cultured from the sputum. An electrocardiogram was normal. X-ray films of the chest showed an enlarged right hilus (Fig. 1). The joints showed changes consistent with both degenerative and rheumatoid arthritis, and there were multiple soft-tissue densities in the extremities and abdomen. The sacrum was eroded in the region of a large, soft-tissue, calcium deposit, with widening and

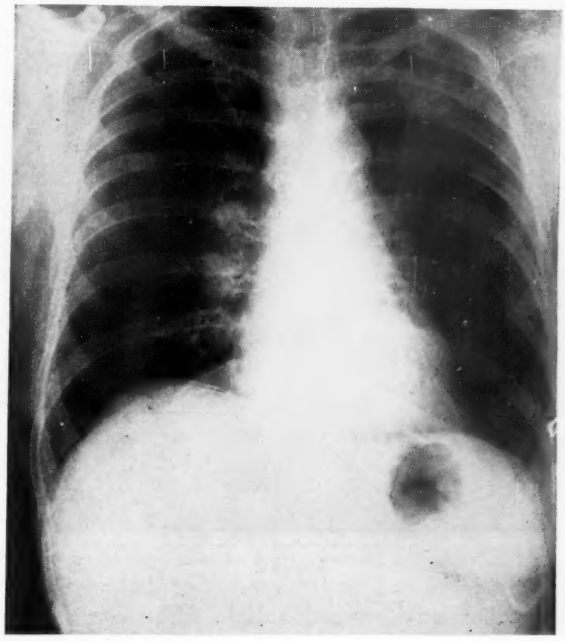

FIGURE 1.

destruction of the left superior sacroiliac joint suggestive of a chronic infectious process (Fig. 2). A barium-enema examination was negative.

Shortly after admission the temperature fell to normal and remained there without specific therapy. The pruritus failed to respond to topical therapy and remained a severe problem throughout the hospital course. The patient was put on a strict low-calcium diet, with a fluid intake of 4 or 5 liters a day. The urinary output was consistently over 2 liters a day, with a calcium content in excess of 200 mg. The blood calcium fell to 12.2 mg., the phosphorus to 4.7 mg., and the nonprotein nitrogen to 49 mg. per 100 cc. The soft-tissue masses gradually decreased in size and became firmer and less fluctuant. Aspiration yielded 8 cc. of thick, yellow fluid, which contained large amounts of calcium. The anemia failed to respond to iron or vitamin therapy, but the hemoglobin rose to 13 gm. per 100 cc. following three transfusions. Stilbestrol therapy was refused by the patient because of nausea. She was discharged ambulatory and much improved on the seventeenth hospital day.

Final admission (two years later). The patient did very well at home for a year and a half on a high-fluid, low-calcium diet. Six months before the second admission she had a severe respiratory infection, with cough, nasal discharge, headache, fever and chills. Following this she began to have hourly urinary frequency during the day and four-to-five-times nocturia. The appetite steadily declined, and fatty-food intolerance became marked.

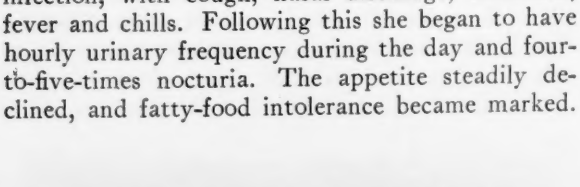

FIGURE 2.

One month before admission she could not tolerate any solid food, began to lose weight rapidly and became so weak that she remained in bed. One week before admission a steady, dull pain began in the right upper quadrant, accompanied by nausea and vomiting. Two days before admission the abdominal pain became generalized, with knife-like exacerbations produced by coughing or deep inspiration. The urine became noticeably darker and the stools, which had been passed regularly throughout the illness, became clay colored.

Physical examination revealed an acutely ill, dehydrated, icteric woman. The chest was clear, and the heart was of normal size, with regular sinus rhythm and a Grade I, apical, systolic murmur. The abdomen was protuberant, with marked tenderness in the right upper quadrant and hypoactive peristalsis of medium pitch. There was no costo-vertebral-angle tenderness.

The temperature was 98.6°F., the pulse 100, and the respirations 24. The blood pressure was 90 systolic, 60 diastolic.

A catheterized urinary specimen showed a specific gravity of 1.016, gave a ++ test for albumin, a + test for bile and a positive Sulkowitch test. Occasional white cells and many bacteria were noted in the sediment. The blood contained 7.5 gm. of hemoglobin and 16,000 white cells. The nonprotein nitrogen was 133 mg., the calcium 7.2 mg., the phosphorus 5.7 mg., and the alkaline phosphatase 10.7 units per 100 cc.; the van den Bergh reaction was 3.6 mg. per 100 cc. direct, 4.6 mg. total, and the serum amylase 28 units per 100 cc. The chloride was 105 milliequiv., the sodium 134.8 milliequiv., the potassium 5.6 milliequiv., and the carbon dioxide 11.6 milliequiv. per liter. The prothrombin time was 26 seconds (normal, 17 seconds), or 50 per cent of normal. X-ray films of the chest showed decrease in the scapular calcification and persistence of the prominent hilar shadows. Plain films of the abdomen showed tremendously increased calcification about the femoral heads, no change in the sacroiliac joint (Fig. 3), and some increase in the intra-abdominal calcification, particularly in the right upper quadrant and around the upper pole of the left kidney.

The patient was given fluids intravenously and 400,000 units of penicillin and 1 gm. of streptomycin each day. The temperature rose briefly to

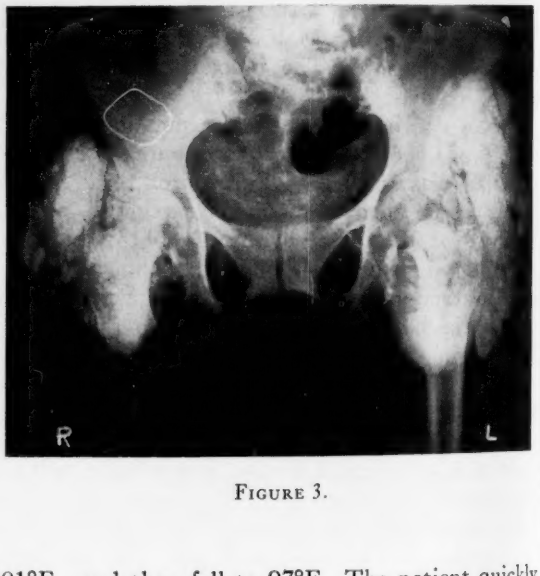

FIGURE 3.

101°F., and then fell to 97°F. The patient quickly lapsed into a semicomatose condition, with Kussmaul breathing, weak pulse and cold extremities. The white-cell count rose rapidly to 62,800, and the nonprotein nitrogen to 155 mg. per 100 cc. The patient died quietly on the third hospital day.

DIFFERENTIAL DIAGNOSIS

DR. MARIAN M. ROPES*: In this long case there are some points that are clear but some that are very difficult to explain, and I cannot interrelate all in one disease. There are many systems involved, and I shall start by discussing them separately. The joint involvement began first thirty-eight years before admission. It is difficult to tell whether

*Associate physician, Massachusetts General Hospital.

all the joint disease represents one disease. At the time of admission, apparently, the patient had the typical physical findings and x-ray support for a diagnosis of rheumatoid arthritis. The first period of the disease from the age of sixteen to forty does not sound much like the average onset of rheumatoid arthritis. However, intermittent attacks of involvement of the knee and one long attack of involvement of the low back, with radiation down the legs, would not be inconsistent with such a diagnosis. The surprising thing would be to have such a long course before progressive disease began. For the last fourteen years she had progressive, deforming arthritis, and I think this course would be unlikely in any of the other so-called generalized connective-tissue diseases or in any of the other joint diseases I would consider. I shall assume that the underlying joint disease, therefore, was rheumatoid arthritis.

The first evidence of involvement other than joint began three years before admission, with the constitutional symptoms of severe weight loss and cough. One year later there was evidence of hilar-lymph-node enlargement, gastritis, blood in the stools and a very severe anemia. Much of this could still be due to an exacerbation of the rheumatoid arthritis. The other possibilities would be sarcoidosis and lymphoma, particularly in view of the hilar enlargement. There is relatively little to support either diagnosis. The x-ray therapy apparently did not alter the lymph nodes, although it did produce some change in the cough.

I wish we knew what the urine showed at the time of admission to the other hospital because, as far as I am concerned, it is impossible to say whether this patient had renal disease before she had the high intake of vitamin D and calcium. It seems probable to me that she did have underlying renal disease, possibly amyloid or some type of nephritis. The renal disease could be due to the vitamin D and calcium intake but it seems more severe than one would expect. The high vitamin D intake surely could have produced some of the findings at the time of the first admission to the hospital. The soft-tissue swellings, with very little evidence of inflammation, are entirely consistent with those seen in vitamin D poisoning. However, apparently some of the swellings disappeared, and I think it would be unlikely for those due to vitamin D toxicity to disappear. Also, the increased anorexia and the tremulousness would fit in very well with vitamin D poisoning. The band keratitis was further evidence. The renal changes could be due just to vitamin D poisoning in the presence of the high calcium intake, but as I have said I think it is likely that there was underlying renal disease. It is interesting to note that the phosphorus was relatively low in proportion to the nonprotein nitrogen and uric acid elevation and is consistent with marked elevation of the calcium, which I am assuming was due to the vitamin D poisoning.

Material containing calcium was withdrawn from one of the masses. Unfortunately, there was no information about what the calcium and phosphorus content of this material was. The withdrawal from any soft-tissue mass of calcium-containing material, which I assume in this case was actually a precipitated calcium salt, is unusual. In our experience masses in the region of the joints have rarely contained precipitated calcium except in several cases of vitamin D poisoning and 2 cases that may have been scleroderma or other disease in the group of the connective-tissue diseases. It is also interesting that the calcium precipitated in the masses in vitamin D poisoning had a ratio quite different from that in bone. The calcium-phosphorus ratio was just twice that found in bone. I have no idea what the significance of this is, but it seems to be rather constant in the cases of vitamin D poisoning. The calcium precipitated here certainly suggests the material frequently withdrawn from the cysts that appear with vitamin D poisoning.

Again one wonders whether the skin lesions, although calcified possibly by the vitamin D poisoning, represented another disease. Although they were not typical they again raise the possibility of sarcoidosis. The x-ray films revealed more confusing findings — hilar-lymph-node enlargement and the sacroiliac-joint lesion that I find extremely difficult to explain. I think it would be well to see the x-ray films at this point.

Dr. Joseph Hanelin: We have two sets of films made two years apart. The first films show enlargement of the lymph nodes at the right hilus, probably minimal left hilar adenopathy and scattered densities within the left lung (Fig. 1). Two years later the right hilar adenopathy is still present, perhaps slightly smaller. The remainder of the chest appears unchanged. However, in the interval changes have occurred at the shoulders. In the earlier films there was a large calcium deposit just below the left humeroscapular joint that is not visible in the later films. However, additional calcium deposits are seen around the upper outer aspect of the humerus.

Dr. Ropes: None of these were present in the earlier films?

Dr. Hanelin: Perhaps a few, but not as marked as in the later films. The abdominal film shows scattered calcium deposits in the upper abdomen and a considerable amount of calcium about the left hip, with smaller deposits about the right hip. There is destructive change in the left sacroiliac joint. The joint space is widened and irregular, and calcifications are present in direct contact with the joint. The right sacroiliac joint, while slightly narrowed, does not show any actual destruction. The precise distribution of the abdominal

calcifications cannot be determined; however, deposits are probably present in the liver and in and about the kidneys. Two years later the abdominal calcifications are more numerous. Quite significant is the change about both hips (Fig. 2 and 3). In the two-year interval the para-articular calcification shows a tremendous increase.

The left sacroiliac lesion has not definitely progressed during this period. How much of the destruction may be due to the calcification in the joint I am not certain. We have seen a case in which there was progressive destruction of a phalanx due to calcium adjacent to it.

DR. ROPES: Are there any joint changes consistent with rheumatoid arthritis?

DR. HANELIN: There are changes in the fingers consistent with it. The phalangeal joints show narrowed interspaces and some hypertrophic changes at the distal joints, with rather similar changes in most of the digits. The changes at both the proximal and distal interphalangeal joints at this particular stage are those of osteoarthritis, which may have been induced by the rheumatoid process.

DR. ROPES: There is nothing to suggest sarcoidosis such as bone cysts?

DR. HANELIN: No; I do not think so. Films of the knee joints show moderate degenerative change, and evidence of considerable muscular wasting.

DR. ROPES: I should say the x-ray films in general do not help me because I find it very difficult to explain the changes in the hips, which are the most disturbing feature in the films. Also, the evidence of rheumatoid arthritis is much less marked than I thought it would be. The clinical story was most consistent with that, and the clinical changes were consistent with a low-grade activity of a rheumatoid arthritis. However, I should judge that it played a relatively small role in the total picture. The response of this patient to low-calcium and high-fluid intake gives, I think, further confirmation of some role played by vitamin D. I think the next year and a half of relative well-being is somewhat against a diagnosis of lymphoma, which can be suggested by some of the findings, or of myeloma, which must be thought of in any patient with skeletal lesions, renal disease and severe anemia. However, there was no positive evidence of this, and I think the course is against it.

When I come to the last illness I find more confusion. The increasing renal failure was apparent, and the patient went on to terminal severe renal failure. It is possible that this was due to residual damage from the vitamin D. However, if as I presume she took no more vitamin D for the two years and was on the low-calcium, high-fluid intake, I would think it very unlikely that the renal failure ensuing so late was due to vitamin D damage to the kidneys and assume that there must have been underlying renal disease. She then developed liver involvement, probably obstructive. Whether or not this was related to the calcifying tissue or whether it was due to stones that were not apparent it is difficult to say. I judge that terminally she also developed some degree of peritonitis.

Now, as I have already said, I find it extremely difficult to put this entire case together. I still think the patient had rheumatoid arthritis as the underlying joint disease. Until I had seen the lack of evidence of joint change by x-ray and the extreme progression of calcification around the femur, I believed that rheumatoid arthritis played a relatively large part in the disease. Now I think it played a small part. There is no question that she had renal disease, which was partly due, I think, to the vitamin D and high-calcium intake; it seems probable that she also had an underlying kidney disease, which could be amyloid or some type of nephritis. In addition to the rheumatoid arthritis she had severe vitamin D poisoning. I believe that the sacroiliac changes were related to the vitamin D intake. However, I find it very difficult to say that all the calcification around the joint remaining after the vitamin D was discontinued was due to just that. There is no question that the other calcium deposits were typical of vitamin D changes and this type of calcification usually does disappear when the vitamin D is stopped. As I have said I cannot explain the persistence of the changes around the femur. The hilar-lymph-node enlargement, too, is disturbing. I would say that of the other possible diagnoses, sarcoidosis would fit as well as any that I can think of, but that would not in any way explain the changes around the hip.

DR. HANELIN: I would like to ask Dr. Ropes whether she has had the opportunity of following the fate of soft-tissue calcifications that result from vitamin D poisoning?

DR. ROPES: We know it disappears in some cases very rapidly, in the first few months after the vitamin D is stopped. It should have disappeared here if the patient really did not continue to take vitamin D. It is possible that she continued to take it, for we know that patients do become addicted to vitamin D. In the cases we have seen both the soft-tissue calcification and that around the joints disappeared very rapidly.

A PHYSICIAN: Would Dr. Ropes care to comment on the icterus, and does she wish to comment on the possibility that this was a low-sodium renal failure?

DR. ROPES: There was some suggestion of loss of sodium but I think not much greater than one would expect in this degree of failure. I assume that the best explanation of the liver involvement is the presence of an inflammatory process in the region of the biliary tract, but I am unable to relate it to the rest of the picture.

Clinical Diagnoses

Uremia.
Vitamin D intoxication leading to chronic nephritis.
Jaundice, cause undetermined.
Anemia, cause undetermined.
Rheumatoid arthritis.

Dr. Ropes's Diagnoses

Rheumatoid arthritis.
Vitamin D intoxication, with generalized calcification.
Chronic nephritis, ?amyloid.
Sarcoidosis of hilar lymph nodes.
Biliary-tract infection, with peritonitis.

Anatomical Diagnoses

Vitamin D intoxication.
Metastatic calcification, generalized, especially in kidney, liver, adrenals, lungs and blood vessels.
Pyelonephritis, chronic, with nephrocalcinosis (and uremia).
Sarcoidosis, pulmonary.
Tuberculosis, active, of lungs, urinary bladder, kidneys and uterus.
Empyema of gall bladder, ruptured, with general peritonitis.
Liver abscesses, multiple, right lobe.
Cholelithiasis.
Subdiaphragmatic abscess, right.
Empyema, right.

Pathological Discussion

Dr. Tracy B. Mallory: This case was extraordinarily complex, and we cannot unravel more than a small portion of it even after the post-mortem examination. Unfortunately, we were faced with restrictions — we had to replace all organs — and a very short period for performance of the post-mortem examination so that we could not do as complete an examination as the interest of the case warranted.

The immediate cause of death is perhaps the easiest thing to dispose of. We found a large abscess cavity in the region where the gall bladder should have been. There was no gall bladder. There was a stone free in the peritoneal cavity and a generalized peritonitis, clear evidence of a ruptured empyema of the gall bladder. Extending from this into the right lobe of the liver were many communicating abscesses, and the process had terminally spread through the diaphragm to produce an empyema of the right pleural cavity. Acute sepsis arising in the biliary tract was evidently the cause of death.

The next point of interest was perhaps the kidneys, which were very small, weighing only 100 gm. The adrenal glands were likewise very atrophic and showed extensive replacement with calcium. The hilar lymph nodes were considerably enlarged but not caseous. There were many fibrous scars throughout the lungs, and the bladder revealed an acute cystitis. Microscopical sections showed that the cystitis was tuberculous. That fits well with the history of dysuria during the terminal phase of life. There was also active tuberculous endometritis, and there were some tubercles in the kidneys. There was very extensive calcification in the kidneys and, I believe, an underlying nephritis, just as Dr. Ropes predicted, but it was so old that I cannot be sure what it was, possibly old pyelonephritis to account for the very marked atrophy. I do not believe the primary renal disease was tuberculosis.

The hilar lymph nodes and many sections of the lung showed quite clear-cut sarcoidosis with asteroid bodies in the giant cells. These bodies are not seen in the Langhans' giant cells of tuberculosis. It is relatively unusual to have both sarcoid and active tuberculosis in the same patient, but I think it is clear that we have that combination here. The lungs likewise demonstrated the most extensive metastatic calcification of the alveolar walls that I have ever seen. Metastatic calcification showed up in many other areas — in blood vessels for instance and especially in the adrenal glands. The cortex was almost entirely replaced by calcareous deposits, and in the sections that we have so far seen there was hardly any visible medulla.

Dr. Benjamin Castleman: Was the adrenal gland tuberculous?

Dr. Mallory: I suppose it could have been a healed tuberculous lesion, but we have no proof, merely this old calcification.

I do not know how to put this together any better than Dr. Ropes did. In severe sarcoidosis, hypercalcemia and rather extensive deposits of calcium in the kidneys and other organs do occur. So we have at least two possible etiologies for the deposits of calcium here, both the hypervitaminosis and the sarcoidosis. Some of the calcified masses could also have represented healed tubercles, but it is my impression that the tuberculosis was terminal. Death was actually caused by an entirely coincidental lesion, sepsis in the biliary tract, with rupture of the gall bladder, liver abscesses and terminal peritonitis.

Dr. Ropes: Did you have a chance to examine the sacroiliac joint to see what the underlying pathologic process was?

Dr. Mallory: No; we did not. I rather strongly suspect that the disease in the sacroiliac joint was tuberculosis. Unfortunately, it has not been proved.

Dr. Hanelin: Was there calcification in the liver?

Dr. Agnes Burt: Yes; there was some.

A Physician: Were the parathyroid glands normal?

Dr. Mallory: They were small and apparently normal. The thyroid was moderately atrophic.

CASE 36372

Presentation of Case

A twenty-nine-year-old man was admitted to the hospital for study.

Eight months before entry the patient developed exertional dyspnea with fatigability, and two months before admission he noted the gradual onset of hoarseness. He was admitted to another hospital, where an x-ray examination disclosed a mass in the left chest. In addition, a paralysis of the left vocal cord was found. The patient had not had cough or sputum, and tests for tuberculosis were said to be negative. A bronchoscopic examination showed narrowing of the left-upper-lobe bronchus, but no tissue was available for biopsy. He was treated with streptomycin for three weeks. He felt well and had a normal appetite, and there was no history of malaise or weight loss.

He had previously been well except for an allergic condition, which began with infantile eczema and progressed to seasonal hay fever and nonseasonal asthma. The dermatitis had improved on vitamin therapy, but the asthma had persisted, requiring repeated administration of epinephrine and Pyribenzamine. In addition he had had an apparently uncomplicated three-week attack of catarrhal jaundice three years before admission. Five or six months before entry, he had a five-day episode of a pleuritic type of pain. This had cleared, and there had been no further chest pain.

Physical examination showed a well nourished man in whom the only positive findings were hoarseness, scattered rales posteriorly, and a scaly, lichenified skin change over the antecubital and popliteal areas.

The temperature, pulse and respirations were normal. The blood pressure was normal.

Examination of the urine was negative. Examination of the blood showed a hemoglobin of 14.8 gm. per 100 cc., and a white-cell count of 8800, with 70 per cent neutrophils, 14 per cent lymphocytes, 3 per cent monocytes, 11 per cent eosinophils and 2 per cent basophils. The serum protein was 7.0 gm. per 100 cc. and the prothrombin time 20 seconds (normal, 17 seconds). An intradermal coccidioidin test was negative after forty-eight hours. A roentgenogram of the chest (Fig. 1) showed considerable elevation of the left hilus and decrease in the size of the left upper lobe. There was an ill defined area of rarefaction 5 cm. in greatest diameter in the left-upper-lung field superimposed on the anterior extremity of the first through the third rib. Comparison with previous films showed this to be the residue of a more clearly defined cavity in which there was a fluid level previously. In and about this region there was linear and hazy mottled density. The left leaf of the diaphragm was elevated and was limited in excursion. The left costophenic angle was obliterated by old pleuritis. There was a slight inspiratory shift of the heart and lower mediastinum toward the left. The major bronchus of the left upper lobe was not visualized and possibly was narrowed. No definite discrete lymph nodes were recognized, but the carina was wide. The right-lung field was grossly clear.

On the fourth hospital day an operation was performed.

Differential Diagnosis

Dr. Helen S. Pittman*: It seems to me that although the past history was interesting — infantile eczema, seasonal hay fever and nonseasonal asthma — and undoubtedly the patient was miserable, it had nothing to do with the present illness. I also think that the three-week attack of catarrhal jaundice can probably be dismissed for the time being. It seems to me that the story began eight months before entry, when the patient developed an exertional dyspnea, and came to a head two months before admission, when he became hoarse and had an x-ray film taken. A man with asthma does not have too good a vital capacity anyway, and that, with a mass and partial collapse of the left upper lobe, would probably explain the exertional dyspnea. I should like to see the x-ray films.

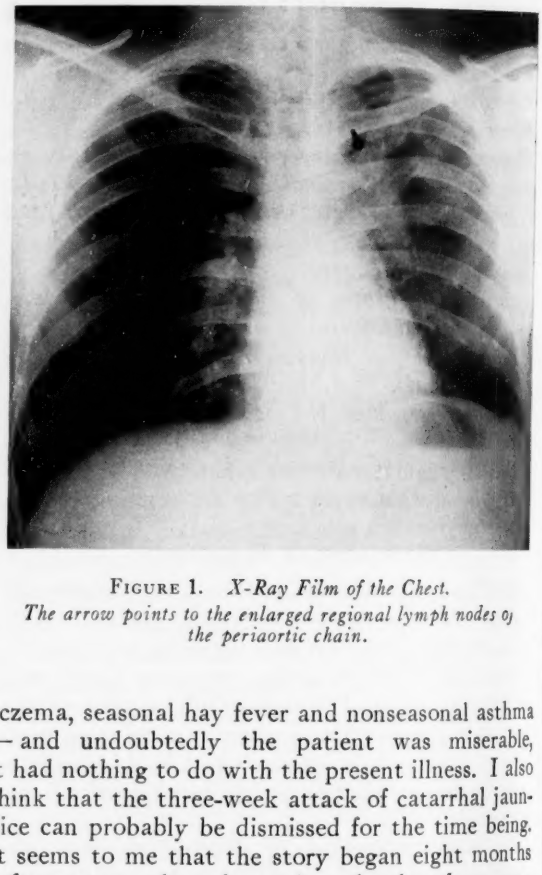

Figure 1. *X-Ray Film of the Chest.*
The arrow points to the enlarged regional lymph nodes of the periaortic chain.

Dr. James J. McCort: The initial films taken at another hospital showed a small fluid-containing cavity in the left upper lobe. On the chest films taken shortly after admission to this hospital there is an irregular area of density in the apicoposterior segment of the left upper lobe. We have evidence that the left upper lobe is somewhat re-

*Associate physician, Massachusetts General Hospital.

duced in size because the hilus is elevated, and the major fissure on the left seems to be displaced upward. Thickening of the pleura over the entire left lung, most marked over the apicoposterior segment, is noted. From the fluoroscopist we have the information that it was thickened pleura and not fluid. The nodular density around the hilus and aortic arch (Fig. 1) indicates lymph-node enlargement of the following groups: the superior and inferior interlobar bronchial lymph nodes and the periaortic lymph nodes. The left paratracheal and left bifurcation groups of nodes may also be enlarged.

Dr. Pittman: It seems to me that there is only one reasonable thing for this patient to have had, but since he was a young man I ought to pay a little attention to other things. I assume that as he had had asthma from an early age he had probably not been in the armed forces, but he must have done some traveling in the West because a coccidioidin test was done quite early in the illness. I have personally seen only 2 cases of coccidiomycosis, and although certainly cavitation may be present I do not think there is likely to be paralysis of the recurrent laryngeal nerve. Tuberculosis was considered, but all tests done at another hospital were said to be negative.

I spoke to Dr. Richard H. Sweet about this problem because the paralysis of the recurrent laryngeal nerve, elevation of the diaphragm and "something" in the chest to me spells carcinoma of the lung and nothing else, even though the patient was only twenty-nine years old and had many other things the matter with him. Dr. Sweet said that in his experience he had seen 2 cases in which there was paralysis of the recurrent laryngeal nerve and of the diaphragm due to tuberculous lymph nodes but that the paralysis in all the other cases was always due to cancer.

We always talk about Friedländer's pneumonia as causing cavitation, and I suppose I ought to mention it.

If one is faced with a problem like this, — a young man who was asthmatic, who had serious disease and who needed the lungs very much to carry on for the rest of his life, — one has to decide how to approach the problem. I think the only safe approach to a situation of this sort is to assume that I am dealing with cancer. I think one can go wrong much less frequently if one jumps to that conclusion, given the paralysis of the diaphragm and of the recurrent laryngeal nerve. Add to that lymph nodes, which Dr. McCort thinks he can see, and the reason for the pressure on the nerves and the paralysis seems apparent. I therefore think that this patient had a carcinoma in the upper lobe and that because of the nerve paralysis it had already invaded the mediastinum and was inoperable. I assume that he was explored with the hope that a lobectomy could be done. I do not believe a pneumonectomy would be planned on an asthmatic patient. I do not believe pneumonectomy would be a life-saving procedure because it would leave him too much crippled. If my diagnosis is correct, I would guess that the surgeon removed some tissue and backed out. Dr. Scannell, I am sure, is waiting to tell me.

Dr. John L. Sosman: The duration of the present illness dated back to two years previously. The patient was to leave for Europe within a few weeks, and as the lesion seemed to clear up he went.

Dr. J. Gordon Scannell: That is correct. There were changes noted in the left upper lobe and inflammation about two years before admission, but since the patient had some travel plans and in the course of a month or six weeks the process cleared quite remarkably, he was allowed to travel. And then the story starts. I wonder if that would help, Dr. Pittman?

Dr. Pittman: I am still very much prejudiced in favor of my diagnosis although I have tried to think of another one. Certainly, from the small lesions we see in the survey films, carcinomas may be present for a long time before they produce symptoms. If the process cleared, the patient probably had some infection that cleared. Of course, I suppose this may have been tuberculosis and another case in which there was nerve paralysis. Tuberculosis would fit the age much better, but I still think a neoplasm is a more likely explanation for it.

Clinical Diagnosis

?Tuberculosis.
?Carcinoma.

Dr. Pittman's Diagnosis

Carcinoma of lung.

Anatomical Diagnosis

Carcinoma of lung, with metastases to regional lymph nodes (at twenty-nine years of age).

Pathological Discussion

Dr. Scannell: We were unwilling to accept a diagnosis of inoperable carcinoma in a patient of this age without positive evidence. There had been a cytologic smear that was consistent with neoplasm. The patient was explored by Dr. Churchill, and the operation limited to an exploratory thoracotomy and biopsy. Occupying the superior mediastinum and breaking out between the upper and lower lobes and into the upper lobe was a large, angry-looking mass of confluent nodular lymph nodes that was surgically out of bounds. The left upper lobe itself was diminished in size and showed very little exchange of air. There was also a good deal of inflammatory change in the left upper lobe.

Dr. Tracy B. Mallory: The biopsy showed a very obvious squamous-cell carcinoma, Grade II.

Dr. Scannell: I believe that two years ago the films would have been read as tuberculosis without any question.

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WANTED — A CO-ORDINATED PLAN

THE presidents of the medical societies of the states that constitute the First Army area — the New England states, New York and New Jersey — were called into conference at Governor's Island on August 17.

On this occasion a virtual ultimatum was issued by the military authorities. A specified number of volunteer medical officers, largely of company grades, were to be procured within the week or the Army would recall into active service from its reserve lists any veterans of World War II that it needed, with or without their consent. The Massachusetts quota was set at 67. The deadline was later extended to August 28, lengthening to eleven days the period between the ultimatum and the consummation of the act.

A meeting was hastily called of representatives of the three medical schools and the major hospitals in Massachusetts, and by unanimous consent the following telegram was sent on August 23 to Secretary of Defense Louis Johnson, Chairman W. Stuart Symington, of the National Security Resources Board, and Senator Millard E. Tydings, chairman of the Senate Armed Services Committee. Copies were sent also to Dr. George F. Lull, general manager of the American Medical Association, Senator Chan Gurney, ranking minority member of the Senate Armed Services Committee, Senator Saltonstall, Senator Lodge, the surgeons general of the Army, Navy and Air Force, and Brigadier General Shambora, First Army Headquarters, Governor's Island, New York:

> Representatives of the three medical schools and of the major hospitals in Massachusetts and the officers of the Massachusetts Medical Society are deeply disturbed by the apparently independent action of the Department of the Army threatening to call up a large number of medical reserve officers on October first unless volunteers are found to replace them. We are eager to co-operate to the utmost in meeting any urgent need of the Army but insist that this be done through fully co-ordinated plans for most effective use of medical, dental, nursing and associated technical personnel for all armed services, civilian defense and civilian medical care.
>
> In our opinion any other policy is shortsighted and hazardous. This action by the Army carries no assurance of co-ordinated policy under the Department of Defense, and if permitted to go into effect will lead to confusion, unfair pressure, poor selection of personnel for overall defense needs, and extravagant waste of expensively trained, none too numerous manpower. We do not feel competent to bring coercion to bear on young men in our jurisdiction to volunteer before a clear-cut manpower policy has been made, and we urge immediate passage of legislation to this end.

This telegram was signed for the group by Leland S. McKittrick, president of the Massachusetts Medical Society.

There is little question from which categories the first groups of medical officers called should be drawn. The really important issue is that the selections should be made according to an orderly and intelligent plan that takes into consideration the over-all present and possible future needs of the nation. The bonus of $100 a month, moreover, offered to medical officers as an inducement to volunteer has assumed with changing circumstances some of the unpleasant features of a bribe, and

might be taken to represent a reflection on the patriotism of a profession whose loyalty has always been beyond question.

A co-ordinated defense, planned by the most capable persons that the country can produce, should be the only one tolerated by the American people, whose lives and freedom are in peril.

EDUCATION ON ALCOHOLISM

THERE is no particular need for calling attention again to the growing problem of alcoholism, except that so important a question needs constant attention if it is to be met squarely and combated resourcefully. As one of the impedimenta of progress it is world wide, although of special importance in the great industrial countries of the temperate zone.

It is not necessary here to go into detailed statistics; in this country are an estimated 65,000,000 persons who "drink," of whom 4,000,000 are problem drinkers. It is these with whom Society is concerned, for alcohol interferes with their satisfactory adjustment to their social and economic life to the degree that, in the latter relation, a $432,000,000 wage loss is sustained annually.

The importance of the problem is enhanced by the fact that the majority of these drinkers can be salvaged. They are not the ultimate derelicts of alcoholism; most of them are employed or are employable; they still have families that are dependent on them; many of them possess exceptional and useful skills.

No one knows better than the physician, who is the confidant of the ill, of the futility of prohibition, the fruitlessness of militant temperance movements or the brutality of treating the alcoholic patient as a criminal. No one knows better than the medical profession that the most important factor in dealing with the public-health problem of alcoholism — as with most social problems — is understanding.

To this end there must be a universal awareness of the factors involved and of the peculiar nature of the disease; its importance, its causes, its insidious character and its treatment. Condemnation of the alcoholic must give way to charity in his misfortune, faith in his rehabilitation and hope for his future.

The National Committee on Alcoholism, through its various affiliates, is trying to accomplish exactly these purposes. It is laboring to develop a public-health program, laying particular emphasis on training of personnel, co-operation of the courts and the moral and financial support of the public.

The Conference on Alcoholism to be held October 3 at the Copley Plaza Hotel in Boston, under the auspices of the Boston Committee For Education on Alcoholism, Inc., represents a tangible effort in the right direction.

TEAMWORK IN PREVENTION OF CONGENITAL SYPHILIS

FOR every physician and organization dealing with pregnancy there is food for thought in a recent editorial* on congenital syphilis.

Surgeon General Leonard A. Scheele stresses the need for teamwork among all individuals and groups concerned with the health of pregnant women. Congenital syphilis is a preventable disease. The cause is known. The methods of detection are known, and the facilities for such detection can be made available. It has been proved that in practically all cases penicillin administered during pregnancy to infected women will prevent syphilis in the child. It is therefore necessary to obtain co-operation of general practitioners, nurses, obstetricians, pediatricians and all organizations — local, state, national — in order to achieve a better record in the prevention of congenital syphilis.

In the last few years the morbidity reporting of primary and secondary syphilis has definitely decreased, but the incidence of congenital syphilis has remained constant. Facilities for serologic tests and the examination of every pregnant woman are definitely better in larger communities, but such facilities should be made available in outlying districts by some organization, local, state or federal.

Congenital syphilis can be prevented. To accomplish this end the co-operation of every physician and every pregnant woman is required in order to eliminate the disastrous results of such infections. Congenital syphilis is a preventable disease and to allow it to continue is a sad commentary on the health program of any country.

*Scheele, L. A. Teamwork. *J. Ven. Dis. Inform.* 31:173, 1950.

AMERICAN ROENTGEN RAY SOCIETY

This year, at its annual meeting in St. Louis, September 26 to 29, the American Roentgen Ray Society will celebrate its fiftieth anniversary. Headquarters for the scientific sessions and commercial exhibits will be the Hotel Jefferson. A committee headed by President-Elect B. P. Widmann, of Philadelphia, is arranging the program, which will include the Caldwell Lecture, delivered by Dr. Henry L. Bockus, professor and chairman of the Department of Internal Medicine at the University of Pennsylvania School of Medicine, whose subject will be "The Role of Roentgenology in Gastroenterology."

Fifty years ago the Society's first meeting was also held in St. Louis, where representatives of the new specialty of roentgenology organized a society for the principal purpose of "the study of the roentgen rays and their application to medicine and science." The program committee is congratulated on its selection of speakers and subjects to commemorate this important anniversary in the progress of medicine in the United States.

The Mayor of Pittsburg, having recently committed a number of vagrants to jail, the Sheriff refused to receive them, and the Mayor arrested him and held him to bail in the sum of $50,000, to answer to the charge of misdemeanor. He refused the prisoners under the advice of the city physicians, who said their reception would be dangerous to the health of the more permanent sick.

Boston M. & S. J., *Sept. 11, 1850*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

Woodworth — John D. R. Woodworth, M.D, of Norwell, died on May 15. He was in his seventy-fifth year.

Dr. Woodworth received his degree from Tufts College Medical School in 1901. He was a member of the Norwell Board of Health and a fellow of the American Medical Association.

His widow, a son and a daughter survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JULY, 1950

Résumé

Disease	July 1950	July 1949	Seven-Year Median
Chancroid	1	3	2*
Chicken pox	475	490	516
Diphtheria	7	23	14
Dog bite	1477	1221	1229
Dysentery, bacillary	9	1	9
German measles	114	121	62
Gonorrhea	186	257	355
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	0	0	1*
Malaria	1	1	15
Measles	1162	394	876
Meningitis, meningococcal	3	5	7
Meningitis, Pfeiffer-bacillus	2	2	2
Meningitis, pneumococcal	2	0	3
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	1	0	0
Meningitis, undetermined	5	1	3
Mumps	383	442	434
Poliomyelitis	19	91	21
Salmonellosis	1	5	11
Scarlet fever	126	91	241
Syphilis	75	140	303
Tuberculosis, pulmonary	203	243	243
Tuberculosis, other forms	13	12	13
Typhoid fever	4	7	4
Undulant fever	3	4	5
Whooping cough	432	387	387

*Six-year median.

Comment

Diseases above the seven-year median included German measles, measles and whooping cough.

Diseases below the seven-year median included diphtheria, mumps, poliomyelitis, salmonellosis, scarlet fever and undulant fever.

Poliomyelitis, with 19 cases, was below the seven-year median and well below the number of cases reported in July, 1949.

Diphtheria had the lowest incidence for the month of July in seven years. Also, the total number of cases in the first seven months of 1950 was lower than that for the comparable period in any year since 1943.

Salmonellosis was lower than for any July in the last fourteen years. A similar low was recorded for June.

Geographical Distribution of Certain Diseases

Diphtheria was reported from: Boston, 1; Chatham, 1; Chelsea, 1; Fall River, 1; Medford, 1; Somerville, 1; Wellesley, 1; total, 7.

Dysentery, bacillary, was reported from: Belchertown, 6; Worcester, 3; total, 9.

Encephalitis, infectious, was reported from; Cambridge, 1; Malden, 2; total, 3.

Infectious hepatitis was reported from: Cambridge, 1; Norwood, 1; total, 2.

Lymphocytic choriomeningitis was reported from; Lowell, 1; Weston, 1; total, 2.

Malaria was reported from: Stoughton, 1; total, 1.

Meningitis, meningococcal, was reported from: Brookline, 1; Medford, 1; Worcester, 1; total, 3.

Meningitis, Pfeiffer-bacillus, was reported from: Boston, 1; Townsend, 1; total, 2.

Meningitis, pneumococcal, was reported from: Boston, 1; Salem, 1; total, 2.

Meningitis, streptococcal, was reported from; Springfield, 1; total, 1.

Meningitis, mumps, was reported from: Norwood, 1; Revere, 1; total, 2.

Meningitis, undertermined, was reported from: Lynn, 1; Springfield, 1; West Springfield, 1; total, 3.

Poliomyelitis was reported from; Essex, 2; Lancaster, 1; Lenox, 1; Medford, 1; Melrose, 1; New Bedford, 1; North Attleboro, 1; North Reading, 1; Pepperell, 1; Saugus, 1; Springfield, 1; Stoneham, 1; Stoughton, 1; Waltham, 1; Wakefield, 1; Weston, 1; Worcester, 2; total, 19.

Salmonellosis was reported from: Waltham, 1; total, 1.

Septic sore throat was reported from: Boston, 3; Lynn, 1; Worcester, 1; total, 5.

Tetanus was reported from: Fitchburg, 1; Middleboro, 1; Wayland, 1; total, 3.

Trichinosis was reported from: Boston, 2; total, 2.

Typhoid fever was reported from: Everett, 1; Holyoke, 1; Watertown, 1; Worcester, 1; total, 4.

Undulant fever was reported from: Dedham, 1; Lowell, 1; Somerville, 1; total, 3.

MISCELLANY

NEW ENGLAND ROENTGEN RAY SOCIETY

The newly elected officers of the New England Roentgen Ray Society for the ensuing year are Dr. George Levene, president, Dr. Jack Spencer, vice-president, Dr. Joseph H. Marks, treasurer, and Dr. L. L. Robbins, secretary. The Society meets on the third Friday of each month, October through May.

CORRESPONDENCE

CLARIFICATION OF PREMARITAL LAW

To the Editor: The recent law of the Commonwealth (Section 28A as amended by Chapter 113 of the Acts of 1950) concerning premarital medical certificates seems to pose some problems for the physician that have in no way been clarified by Dr. Fiumara's communication in the August 10 issue of the *Journal*. As of May 21, 1950, the physician must " . . . certify on forms provided by said department that the applicant therein named has been given an examination, including a serological test for syphilis, on a day specified in the statement, and that, in the opinion of the physician, the person therein named is not infected with syphilis, or, if so infected is not in a stage which is communicable, but if such infection is communicable, no such certificate shall be issued . . . Whoever, being subject to the laws of the Commonwealth, fails to comply with any provision of this section shall be punished by a fine of not less than ten nor more than one hundred dollars."

This represents quite a departure from the previous law, which, according to the Commissioner of Public Health at the time, "requires only a laboratory test for syphilis." The issue that I raised at the time, relative to pelvic examinations (*New Eng. J. Med.* **225**:556, 1941), was evaded by both the Commissioner and the Attorney General. The inference from the correspondence published in this journal was that it was desirable to examine the parties in addition to doing a blood Hinton test, but the extent of the examination was left to the imagination of the physician. But now we are apparently subject to a fine if we fail to detect communicable syphilis in the affianced. If the genitals and urethral mucosa of the male show no syphilitic lesions and if his serologic test is negative the physician will probably exonerate him with reasonable confidence. The problem is more complex in the case of the female. There are still many social taboos in the lay mind regarding the genital examination of alleged virgins. The public may be educated up to premarital blood tests, but it still resents a pelvic examination when it has been led to believe that only a blood test is necessary. And even a large segment of the medical population is unaware of this new law. Nor is this ostrich-like attitude on the part of the laity improved by the physicians who are willing to issue the required certificates based merely on a blood test and the naïve hope that the lady has no genital lesions because she has not reported any. But even if the lay public is educated up to premarital pelvic examinations (only a small proportion to date), the physician will still be faced with the problem of excluding syphilitic lesions of the cervix or vagina. This is manifestly difficult as most syphilologists agree. Yet the unhappy physician is by implication subject to a fine of $10 to $100 if he issues a premarital medical certificate to someone with infectious seronegative syphilis. It is to be hoped that, if any practicing physicians had a hand in framing this law, they will inform the rest of us how this problem is to be met and exactly what sort of examination is meant by the term "complete physical examination" referred to in paragraph 3, page 2, of the April, 1950, *Bulletin of Venereal Disease* distributed by the Massachusetts Department of Public Health. Dr. Fiumara uses the term "careful physical examination" in the communication referred to above but fails to face the issue of premarital pelvic examinations. If it is the intention of his department that pelvic examinations be done, in all fairness to the rest of us it seems as if an educational campaign to enlighten Massachusetts maidens what to expect should be initiated.

ALLEN S. JOHNSON, M.D.

Springfield, Massachusetts

BOOK REVIEW

Metabolism and Function: A collection of papers dedicated to Otto Meyerhof on the occasion of his 65th birthday. Edited by D. Nachmansohn, M.D. 4°, cloth, 348 pp., illustrated. New York: Elsevier Publishing Company, Incorporated, 1950. $7.00.

This memorial volume, in honor of Professor Meyerhof, formerly of Berlin, Heidelberg, and Paris, and now research professor of physiologic chemistry at University of Pennsylvania School of Medicine, consists of thirty-eight articles contributed by specialists of Europe and America. The United States is well represented.

Professor Meyerhof received his degree in medicine from Heidelberg in 1909 and joined the faculty of the University of Kiel in 1913. He became interested in cellular physiology, especially energy transformations. After he was appointed a professor at Kiel, he began his brilliant work on muscular contraction, for which he received the Nobel Prize in 1923, jointly with A. V. Hill, of London.

The series of papers is divided into four parts: muscle, nerve, drug action and intermediate metabolism. The part on metabolism comprises half the volume. The book is well published, except for the lack of an index, which detracts from its reference value. The printing was done in the Netherlands, and the complete text was published originally in the *Biochimica et biophysica acta* (Vol. 4, pp. 1-348, 1950), from which it has been reprinted. The volume is not copyrighted in England or the United States, but the publishers forbid the reproduction of any part in any form, including photostat or microfilm. This last provision constitutes a direct hindrance to the advance of knowledge, and the reviewer cannot understand how it can be enforced in noncopyrighted material, unless the original material was copyrighted in Holland under international law. The book should be in all collections on physiology and biochemistry.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Microphthalmos and Anophthalmos with or without Coincident Oligophrenia: A clinical and genetic-statistical study. By Torsten Sjogren and Tage Larsson. 8°, paper, 103 pp., with 20 tables. Copenhagen, Denmark: Ejnar Munksgaard, 1949. 15 Swed. Crowns. (*Acta Psychiatrica et Neurologica*, Supplementum 56.)

The Treatment and Prophylaxis of Syphilis: Arsenobismuth, mercury and fever therapy. By Joseph E. Moore and Harry Eagle. 4°, paper, 31 pp., with 2 tables. *Penicillin Therapy.* By Harold A. Tucker. 4°, paper, 26 pp., with 2 tables. *Ulcer of the Stomach, Duodenum and Jejunum.* By Ralph C. Brown. 4°, paper, 18 pp. *Vitamins and Vitamin Deficiencies* (continued). *Vitamin* B_{12}. By Tom D. Spies. 4°, paper, 8 pp., with 4 illustrations. *The Toxic and Organic Reaction Types of Mental Disease.* By Franklin G. Ebaugh. 4°, paper, 77 pp. *Streptomycin in the Treatment of Infections.* By Chester S. Keefer, M.D. 4°, paper, 43 pp. *Lipidoses: Diseases of the cellular lipid metabolism.* By Siegfried J. Thannhauser, M.D. 4°, 595 pp., with 51 tables. New York: Oxford University Press, 1949. (Reprints from *Oxford Loose-Leaf Medicine.*)

These reprints from *Oxford Loose-Leaf Medicine* are prepared for the convenience of subscribers and are not for sale. The monograph of Dr. Thannhauser is particularly interesting since it presents an up-to-date survey of the lipidoses.

NOTICES

MASSACHUSETTS CHAPTER, AMERICAN ACADEMY OF GENERAL PRACTICE

The Massachusetts Chapter of the American Academy of General Practice will hold its annual meeting in Boston on October 3 and 4. The session will open with a theater party on the first day, followed by clinics on the following morning, a luncheon at the Hotel Kenmore and lectures in the afternoon.

PROGRAM

9:00 a.m. – 12 m. Clinics, Boston City Hospital, by the staff.

12:30 p.m. Hotel Kenmore. Buffet luncheon.

2:30 p.m. Hotel Kenmore. Adolescent Problems. Dr. John Milne Murray, professor of clinical psychiatry, Boston University School of Medicine.

3:30 p.m. Coronary Insufficiency. Dr. Samuel Proger, director, Joseph H. Pratt Diagnostic Hospital, New England Medical Center.

4:30 p.m. Business meeting.

CONFERENCE ON ALCOHOLISM

The Second Annual Conference on Alcoholism will be held on Tuesday, October 3, at the Copley Plaza Hotel in Boston, beginning at noon. The conference, to be held under the auspices of the Boston Committee for Education on Alcoholism, will this year feature "Industry and Alcoholism" as the main topic.

Tickets for the conference may be obtained by application to the Boston Committee for Education on Alcoholism at 417 Boylston Street, Boston (Telephone KEnmore 6-1954).

MASSACHUSETTS SOCIETY OF ANESTHESIOLOGISTS

A meeting of the Massachusetts Society of Anesthesiologists will be held in the auditorium of the Springfield Hospital, Springfield, on Tuesday, October 10, at 8 p.m. The scientific program will consist of a symposium on obstetric anesthesia, the subjects and authors being as follows:

Spinal Anesthesia for Obstetric Anesthesia. H. L. Strachan, M.D.

Combined Anesthesia for Breech Delivery. A. G. Galuszka, M.D.

Resting Spinals in Obstetrics. P. G. Sanderson, M.D.

NEW YORK ACADEMY OF MEDICINE

The New York Academy of Medicine will hold its twenty-third Graduate Fortnight from October 9 to 20.

The program, which will be on the musculoskeletal system, will consist of morning panel discussions, afternoon hospital clinics, evening addresses and scientific exhibits and demonstrations.

COURSE IN TREATMENT OF PARAPLEGIA

A course in the treatment of paraplegia will be given at Cushing Veterans Administration Hospital, Framingham, Massachusetts, on alternate Wednesday evenings, beginning on November 29. There will be twelve sessions in all, each beginning at 7:30 o'clock and lasting for two hours and a quarter.

The course will be given by the staff of the Paraplegia Service, with the assistance of other members of the hospital's full-time and consulting staffs. It will be open to all physicians without cost. Those interested should communicate, before November 1, with Dr. H. S. Talbot, chief, Paraplegia Service, Cushing Veterans Administration Hospital, Framingham, Massachusetts.

RESIDENCY APPOINTMENTS IN PSYCHIATRY AND NEUROLOGY

Applications for appointments as resident in psychiatry in the hospitals and clinics of the Veterans Administration in metropolitan Boston are invited. This is an associated three-year program offered at the Cushing, Framingham, Bedford and West Roxbury hospitals and the Veterans Administration Mental Hygiene Clinic in Boston. Affiliations for child psychiatry are in effect with the Children's Service of Massachusetts General Hospital, with the James Jackson Putnam Children's Center and with the Habit Clinic. The entire program is under the supervision of the Deans Subcommittee on Neuropsychiatry, composed of the professors of psychiatry at Boston University, Harvard and Tufts.

Appointments are made for one year (on July 1, and at such other times as vacancies exist), renewable for a total of three years. The services are rotating, and include one year of closed-ward psychiatry and six months each of open-ward psychiatry, outpatient psychiatry, psychosomatic medicine or child psychiatry, and neurology. Arrangements can be made (independently, by the resident) for training in psychoanalytic psychiatry at the Boston Psychoanalytic Institute.

Applications are invited also for appointments in neurology. The full training here is offered at Cushing Veterans Administration Hospital.

The stipend offered is $2400, $2700 and $3000, for the first, second and third years respectively.

Further information and applications may be obtained from Dr. Jackson M. Thomas, 311 Beacon Street, Boston 16, Massachusetts.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 18–27. International Congress of Psychiatry. Page 240, issue of August 10.

SEPTEMBER 26–29. American Roentgen Ray Society. Page 240, issue of August 10.

SEPTEMBER 27. American Medical Writers' Association. Page xi, issue of July 13.

SEPTEMBER 27–29. Mississippi Valley Medical Society. Page 991, issue of December 15.

OCTOBER 3. Massachusetts Academy of General Practice. Boston City Hospital and Hotel Kenmore.

OCTOBER 3. Conference on Alcoholism. Notice above.

OCTOBER 3 AND 4. Massachusetts Chapter, American Academy of General Practice. Notice above.

OCTOBER 6–MAY 11. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 324, issue of August 24.

OCTOBER 9–20. New York Academy of Medicine. Notice above.

OCTOBER 10. Massachusetts Society of Anesthesiologists. Notice above.

OCTOBER 12–14. American Association of Blood Banks. Page 428, issue of March 16.

OCTOBER 13. Chemotherapy — New Preparations, Their Efficacy and Effects. Dr. Chester S. Keefer. Pentucket Association of Physicians, 8:30 p.m. Haverhill.

OCTOBER 14–19. American Academy of Pediatrics. Page 962, issue of June 15.

OCTOBER 23–27. American College of Surgeons. Page xi, issue of June 29.

OCTOBER 23–28. Medicomilitary Symposium for Officers of Fourth Naval District. Page 34, issue of July 6.

OCTOBER 28. Massachusetts Association of Medical Technologists. Page 324, issue of August 24.

OCTOBER 30–NOVEMBER 3. American Public Health Association. Page 240, issue of August 10.

OCTOBER 31–NOVEMBER 3. International College of Surgeons. Page 170, issue of July 27.

NOVEMBER 1. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

NOVEMBER 1. Hampshire District Medical Society. Page 170, issue of July 27.

NOVEMBER 5 AND 6. American Society for the Study of Arteriosclerosis. Page 170, issue of July 27.

NOVEMBER 6–8. New England Postgraduate Assembly. Hotel Statler, Boston.

NOVEMBER 10. American Trudeau Society. Page 280, issue of August 17.

JANUARY 31. American Academy of Orthopaedic Surgery (see Kappa Delta Award for Research in Orthopedic Surgery). Page 736, issue of May 4.

APRIL 9–13. American College of Physicians. Page 962, issue of June 15.

MAY 24–26. American Goiter Association. Columbus, Ohio.

DISTRICT MEDICAL SOCIETY

HAMPSHIRE

NOVEMBER 1. 4:30 p.m. Northampton State Hospital.
JANUARY 3. 4:30 p.m. Veterans Administration Hospital, Northampton.
MARCH 7. 4:30 p.m. Cooley-Dickinson Hospital, Northampton.
MAY 2. 4:30 p.m. Annual Meeting. Jones Library, Amherst.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 21

FRIDAY, SEPTEMBER 22

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.
*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street, Boston.
*1:30 p.m. Tumor Clinic. Out-Patient Department. Mount Auburn Hospital, Cambridge.

(Notices concluded on page xv)

NOTICES (*Concluded from page 430*)

MONDAY, SEPTEMBER 25

*11:30 a.m.–12:15 p.m. Clinical Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

5:15 p.m. Staff Meeting. Harris Hall, New England Deaconess Hospital.

TUESDAY, SEPTEMBER 26

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

WEDNESDAY, SEPTEMBER 27

*12:00 m.–1:00 p.m. Grand Rounds. Amphitheater, Children's Hospital.

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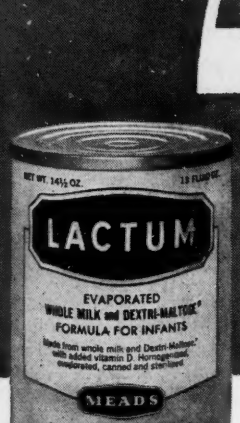

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